FORM PTO 1390
(REV 5-93) US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY DOCKET NUMBER
2001-1187A

U.S. APPLICATION NO.
(if known, see 37 CFR 1.5)
[NEW] 09/914264

International Application No.	International Filing Date	Priority Date Claimed
PCT/GB00/00686	February 25, 2000	February 26, 1999

Title of Invention
PLATINUM (II) COMPOUNDS

Applicant(s) For DO/EO/US
Gordon LOWE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.

3. [X] This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [ ] A translation of the International Application into English (35 U.S.C. §371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19.

9. [X] An **unexecuted** oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)). **ATTACHMENT A**

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment. **ATTACHMENT B**

    [ ] A SECOND or SUBSEQUENT preliminary amendment.

14. [X] Other items or information:

    a. Cover Page of Published International Application No. WO00/50431 - **ATTACHMENT C**

    b. International Search Report - **ATTACHMENT D**

U.S. APPLICATION NO. [NEW] 09/914264	INTERNATIONAL APPLICATION NO. PCT/GB00/00686	ATTORNEY'S DOCKET NO. 2001-1187A

15. [X] The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		
Neither international preliminary examination fee nor international search fee paid to USPTO and International Search Report not prepared by the EPO or JPO $1000.00		
International Search Report has been prepared by the EPO or JPO ..... $ 860.00		
International preliminary examination fee not paid ot USPTO but international search paid to USPTO ..... $ 710.00		
International preliminary examination fee paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $ 690.00		
International preliminary examination fee paid ot USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate		
Total Claims	10 -20 =	0	X $18.00		
Independent Claims	2 - 3 =	0	X $80.00		
Multiple dependent claim(s) (if applicable)			+ $270.00		
TOTAL OF ABOVE CALCULATIONS =				$860.00	
[X] Small Entity Status is hereby asserted. Above fees are reduced by 1/2.				$430.00	
SUBTOTAL =				$430.00	
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					
TOTAL NATIONAL FEE =				$430.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 per property +					
TOTAL FEES ENCLOSED =				$430.00	
				Amount to be refunded	$
				Amount to be charged	$

a. [X] A check in the amount of $ 430.00 to cover the above fees is enclosed. A duplicate copy of this form is enclosed.

b. [ ] Please charge my Deposit Account No. 23-0975 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [ ] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

19. CORRESPONDENCE ADDRESS

000513

PATENT TRADEMARK OFFICE

By: _____
Matthew Jacob ,
Registration No. 25,154

WENDEROTH, LIND & PONACK, L.L.P.
2033 "K" Street, N.W., Suite 800
Washington, D.C. 20006-1021
Phone:(202) 721-8200
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August 24, 2001

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEE FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975.

[CHECK NO. 46118]

[2001-1187A]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Gordon LOWE : **Attn: BOX PCT**

Serial No. [NEW] : **Docket No. 2001-1187A**

Filed August 24, 2001 :

PLATINUM (II) COMPOUNDS :
[Corresponding to PCT/GB00/00686
Filed February 25, 2000]

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents,
Washington, DC 20231

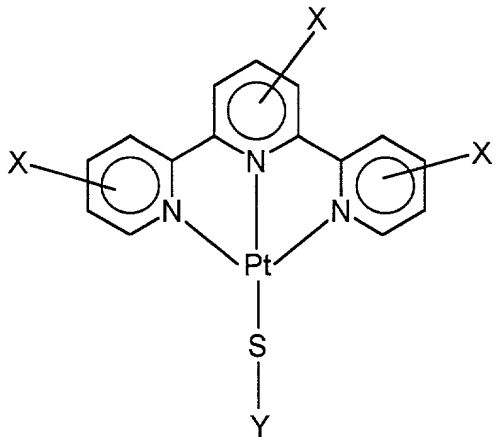
Sir:

In the interest of compact prosecution, please amend the present application as follows:

IN THE SPECIFICATION:

Please replace the paragraph beginning at line 7 and ending at line 19 on page 1 of the specification with the following rewritten paragraph:

In a first aspect the present invention provides a compound which is a complex formula (I), or an isomer thereof,



(I)

wherein

ATTACHMENT B

Please replace the paragraph beginning at line 22 on page 3 of the specification with the following rewritten paragraph:

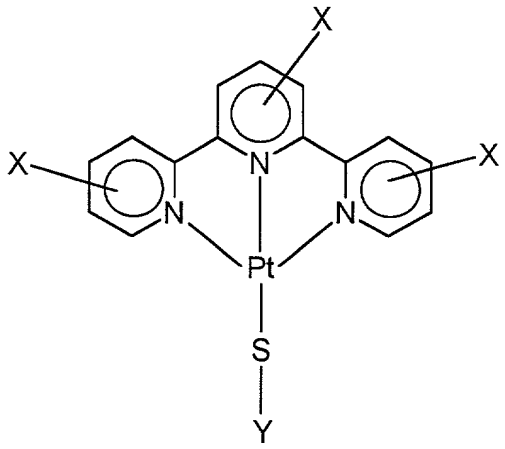
X is preferably hydrogen, halogen such as chlorine, alkoxyl such as methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl or octyloxyl, preferably ethoxyl, butyloxyl, hexyloxyl or oxtyloxyl, or aryl such as bromophenyl or tolyl. A substituent may preferably be at the 4' position of the terpyridine system.

Please replace the paragraph beginning at line 9 on page 4 of the specification with the following rewritten paragraph:

X is hydrogen, halogen such as chlorine, alkoxyl such as methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl or octyloxyl, preferably ethoxyl, butyloxyl, hexyloxyl or octyloxyl, or aryl such as bromophenyl or tolyl; and

Please replace the paragraph beginning at line 31 on page 10 and ending at line 12 on page 11 of the specification with the following rewritten paragraph:

In a further aspect the present invention provides a compound which is a complex of the formula (I), or an isomer thereof,



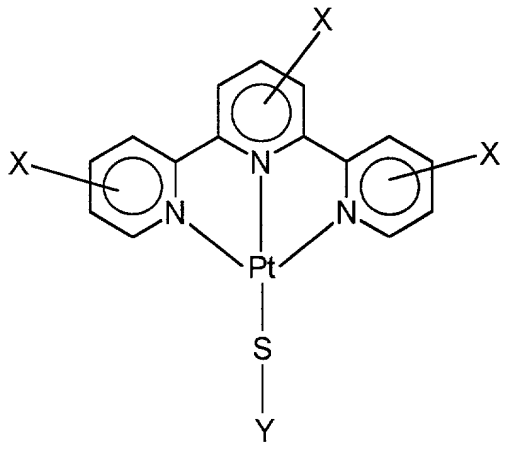
(I)

wherein

IN THE CLAIMS:

Please amend claims 1 to 5 and 7 as follows:

1. **(Amended)** A compound which is a complex of formula (I), or an isomer thereof,



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, alkylthio, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

2. **(Amended)** A compound as claimed in claim 1 wherein X is hydrogen, halogen or alkoxyl or aryl.

3. **(Amended)** A compound as claimed in claim 1 wherein X is hydrogen, chlorine, methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl, octyloxyl, bromophenyl or tolyl.

4. **(Amended)** A compound as claimed in claim 1 wherein Y is alkyl, aralkyl, heterocyclyl or an inorganic oxyacid or inorganic oxyacid derivative.

5. **(Amended)** A compound as claimed in claim 1 wherein Y is $(CH_2)_nOH$ or $(CH_2)_nNH_3^+$ wherein n is an integer of 1 to 6 or alkyl substituted by one or more amino or carboxy groups; CH_2aryl; a 5- or 6-membered saturated heterocyclic ring or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring; or SO_3R or PO_3R_2 wherein R is hydrogen or alkyl.

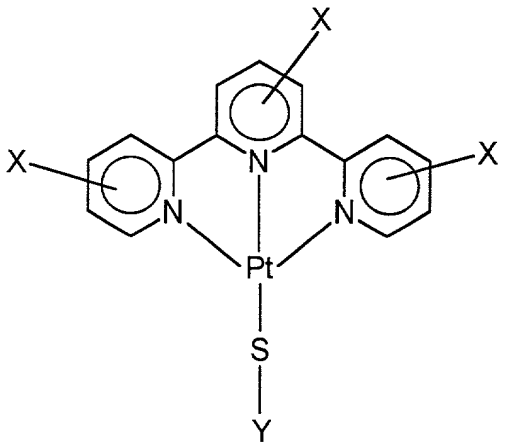
7. **(Amended)** A compound as claimed in claim 1 which is
2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (Il),
2-hydroxyethanethiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
2-aminoethanethiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
imidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
N,S-bis[(2,2':6',2"-terpyridine)platinum(II)] thioacetimine,
N,S-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)] thioacetimine,
diethylphosphorothiolato (4'-chloro-2,2':6',2"-terpyridine)platinum(II),
succinylthiolatoplatinum (II) 2,2':6',2"-terpyridine, or
1-thio-β-D-glucose(2,2':6',2"-terpyridine)platinum (II).

Please cancel claim 8 without prejudice to the subject matter thereof.

Please amend claims 9 and 10 as follows:

9. **(Amended)** A compound which is a complex of formula (I) or an isomer thereof



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, with the proviso that the complex of formula (I) is not 2-hydroxyethanethiolate(2,2':6',2"-terpyridine)platinum (II) or 2-aminoethanethiolate(2,2':6',2"-terpyridine)platinum (II).

10. **(Amended)** A pharmaceutical composition comprising a compound as defined in claim 1 in association with a pharmaceutically acceptable carrier or excipient.

REMARKS

The above amendment re-presents the amendments to the specification and claims made during International Preliminary Examination.

Further, multiple dependency, including improper multiple dependent claims, have been eliminated.

Lastly, non-statutory use claim 8 has been deleted.

Favorable action on the merits is now requested.

Respectfully submitted,

Gordon LOWE

By _____
Matthew Jacob
Registration No. 25,154
Attorney for Applicant

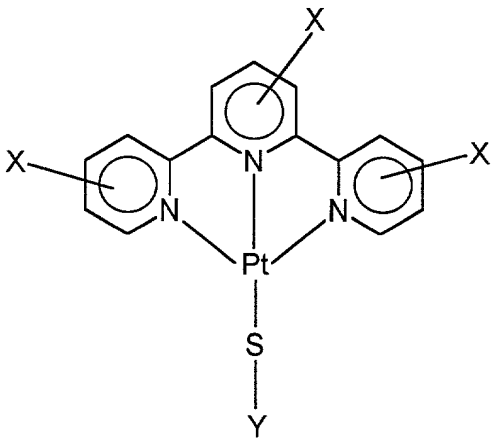
MJ/pjm
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
August 24, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at line 7 and ending at line 19 on page 1 of the specification has be rewritten as follows:

In a first aspect the present invention provides a compound which is a complex formula (I), or an isomer thereof,



(I)

wherein

The paragraph beginning at line 22 on page 3 of the specification has been rewritten as follows:

X is preferably hydrogen, halogen such as chlorine, alkoxyl such as methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl or octyloxyl, preferably ethoxyl, butyloxyl, hexyloxyl or oxtyloxyl, or aryl such as bromophenyl or tolyl. A substituent may preferably be at the 4' position of the terpyridine system.

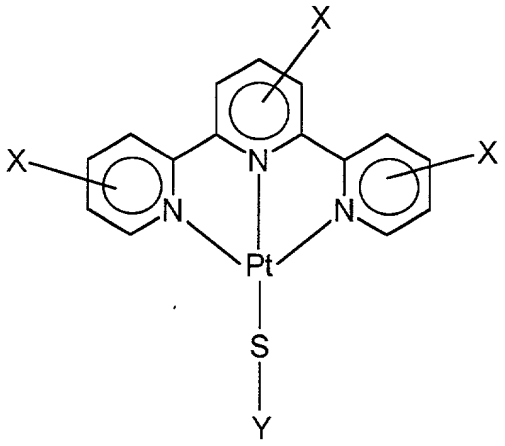
The paragraph beginning at line 9 on page 4 of the specification has been rewritten as follows:

X is hydrogen, halogen such as chlorine, alkoxyl such as methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl or octyloxyl, preferably ethoxyl, butyloxyl,

hexyloxyl or octyloxyl, or aryl such as bromophenyl or tolyl; and

The paragraph beginning at line 31 on page 10 and ending at line 12 on page 11 of the specification has been rewritten as follows:

In a further aspect the present invention provides a compound which is a complex of formula (I), or an isomer thereof,



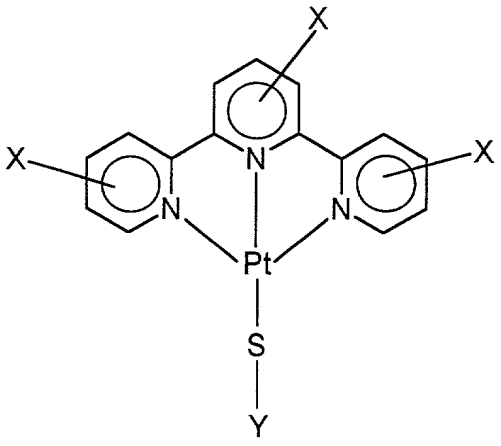
(I)

wherein

IN THE CLAIMS:

Claims 1 to 5, 7 and 9 to 10 have been amended as follows:

1. **(Amended)** A compound which is a complex of formula (I), or an isomer thereof,



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, alkylthio, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

2. (**Amended**) A compound as claimed in claim 1 wherein X is hydrogen, halogen or alkoxyl <u>or aryl</u>.

3. (**Amended**) A compound as claimed in claim 1 [or 2] wherein X is hydrogen, chlorine, methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl, octyloxyl, bromophenyl or tolyl.

4. (**Amended**) A compound as claimed in [any one of claims] <u>claim</u> 1 [to 3] wherein Y is alkyl, [alkaryl] <u>aralkyl</u>, heterocyclyl or an inorganic oxyacid or inorganic oxyacid derivative.

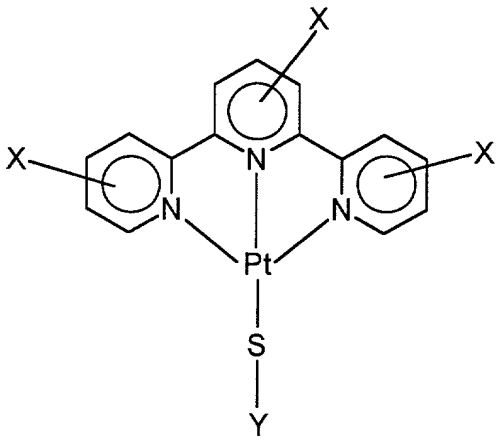
5. (**Amended**) A compound as claimed in [any one of the preceding claims] <u>claim 1</u> wherein Y is $(CH_2)_nOH$ or $(CH_2)_nNH_3^+$ wherein n is an integer of 1 to 6 or alkyl substituted by one or more amino or carboxy groups; CH_2aryl; a 5- or 6-membered saturated heterocyclic ring or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may

be fused to a 6-membered aryl ring; or SO_3R or PO_3R_2 wherein R is hydrogen or alkyl.

7. **(Amended)** A compound as claimed in [any one of claims] claim 1 [to 5] which is
2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (Il),
[2-hydroxyethanthiolate] 2-hydroxyethanethiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine) platinum (II),
[2-hydroxyethanthiolate] 2-hydroxyethanethiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
2-aminoethanethiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),

pyrimidine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
imidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
N,S-bis[(2,2':6',2"-terpyridine)platinum(II)] thioacetimine,
N,S-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)] thioacetimine,
[diethylphosphorothioato]
diethylphosphorothiolato (4'-chloro-2,2':6',2"-terpyridine)platinum(II),
succinylthiolatoplatinum (II) 2,2':6',2"-terpyridine, or
1-thio-β-D-glucose(2,2':6',2"-terpyridine)platinum (II).

9. **(Amended)** A compound which is a complex of formula (I), or an isomer thereof,



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

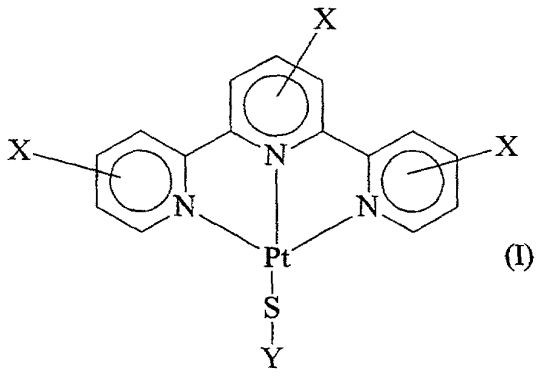
a pharmaceutically acceptable salt thereof, with the proviso that the complex of formula (I) is not 2-hydroxyethanethiolate(2,2':6',2"-terpyridine)platinum (II) or 2-aminoethanethiolate(2,2':6',2"-terpyridine)platinum (II).

10. **(Amended)** A pharmaceutical composition comprising a compound as defined in [any one of claims] claim 1 [to 7 or 9] in association with a pharmaceutically acceptable carrier or excipient.

PLATINUM (II) COMPOUNDS

The present invention relates to platinum (II) compounds for use in the treatment of the human or animal body. The invention in particular relates to 2,2':6',2"-terpyridine platinum (II) compounds for use as anti-protozoal, anti-rheumatoid arthritic or anti-tumour agents.

In a first aspect the present invention provides a compound which is a complex of formula (I)



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, alkylthio, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The term "alkyl" as used herein includes both unsubstituted and substituted, straight and branched chain radicals. Typically it is C_1-C_6 or C_1-C_8 alkyl, preferably C_1 - C_4 alkyl, for example methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl. It may also be pentyl, hexyl, heptyl, octyl and the various branched chain isomers thereof. When the alkyl group is substituted it typically bears one or more substituents selected from aryl, cycloalkyl, halogen, trihaloalkyl such as trifluoromethyl, hydroxy, alkoxy, aralkoxyl, amino, mono or dialkylamino, carbonyl and carboxy.

The term "cycloalkyl" as used herein typically means a cycloalkyl group having 3 to 8 carbons, for example cyclopropyl and cyclooctyl. A cycloalkyl group may be unsubstituted or substituted as the alkyl groups above.

The term "alkenyl" as used herein includes unsubstituted and substituted, straight and branched chain radicals having one or more double bonds. Typically it is C_2 - C_6 alkenyl such as, for example, allyl, butenyl, butadienyl, pentenyl or hexenyl. When the alkenyl group is substituted it typically bears one or more substituents as defined above for the alkyl groups.

The term "cycloalkenyl" as used herein typically means a cycloalkenyl group having 4 to 8 carbons, for example cyclopentenyl or cyclooctadiene.

The term "alkynyl" as used herein includes unsubstituted and substituted, straight and branched chain radicals having one or more triple bonds. Typically it is C_2 - C_6 alkynyl, such as butynyl. When the alkynyl group is substituted it typically bears one or more substituents as defined above for the alkyl groups.

The term "aryl" as used herein includes both monocyclic and bicyclic aromatic groups which typically contain from 6 to 10 carbons in the ring portion, such as phenyl or naphthyl. The aryl group is unsubstituted or substituted. When it is substituted the aryl group may be substituted by one or more substituents selected from C_1-C_6, alkyl, C_1-C_6 alkoxyl, trihaloalkyl such as trifluoromethyl, halogen and hydroxy.

The term "heterocyclyl" as used herein is typically a 3- to 7-membered,

saturated or unsaturated heterocyclic ring containing at least one heteroatom selected from N, O and S and which is optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocyclic ring or to an aryl group as defined above. The heterocyclic ring may be, for example, pyridine, furan, thiophene, pyrrole, pyrimidine, pyrazine, pyridazine, pyrazole or indazole, or a cyclic ether such as glucose.

The term "aralkyl" as used herein refers to alkyl groups as previously defined having an aryl substituent, for example benzyl, phenethyl, diphenylmethyl and triphenylmethyl.

The term "alkaryl" as used herein refers to aryl groups as previously defined having an alkyl substituent.

The term "acyl" as employed herein includes alkyl, aryl and heterocyclyl as described above linked to a carbonyl group.

The term "halogen" as used herein means fluorine, chlorine, bromine and iodine.

The term "alkoxyl" or "aralkoxyl" as used herein includes any of the above alkyl, cycloalkyl or aralkyl groups linked to an oxygen atom.

In accordance with the conventional nomenclature for terpyridine ring systems simple numbering is used for the left hand ring of the terpyridine in formula (I), numbering qualified by prime (') is used for the central ring and numbering qualified by double prime (") is used for the right hand ring.

X is preferably hydrogen, halogen such as chlorine, alkoxyl such as methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl or octyloxyl, preferably ethoxyl, butyloxyl, hexyloxyl or octyloxyl, or aryl. A substituent may preferably be at the 4' position of the terpyridine system.

Y may be substituted with one or more electron withdrawing groups such as a halogen, hydroxyl, carbonyl, amide or carboxyl and/or one or more electron donating groups. Y is preferably alkyl, for example, $(CH_2)_nOH$ or $(CH_2)_n NH_3^+$ wherein n is an integer of 1 to 6, or alkyl substituted by one or more amino or carboxy groups; aralkyl, for example arylCH_2 such as benzyl; heterocyclyl , for example, a 5- or 6-membered saturated heterocyclic ring such as a deoxy-glucose, for instance deoxy-β-

D-glucose or deoxy-glucose substituted by one or more groups such as acyl groups, or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring, for example, pyridyl such as 2-pyridyl or 4-pyridyl, pyrimidyl such as 2-pyrimidyl, imidazolyl such as 2-imidazolyl, or benzimidazolyl such as 2-benzimidazolyl; or an inorganic oxyacid or inorganic oxyacid derivative such as SO_3R or PO_3R_2 wherein R is hydrogen or alkyl. In one embodiment n is an integer of at least 2.

Preferred complexes of formula (I) are those wherein:

X is hydrogen, halogen such as chlorine, alkoxyl such as methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl or octyloxyl, preferably ethoxyl, butyloxyl, hexyloxyl or octyloxyl, or aryl; and

Y is alkyl, for example, $(CH_2)_nOH$ or $(CH_2)_n NH_3^+$ wherein n is an integer of 1 to 6, alkyl substituted by one or more amino or carboxy groups; aralkyl, for example $arylCH_2$ such as benzyl; heterocyclyl, for example, a 5- or 6-membered saturated heterocyclic ring such as a deoxy-glucose, for instance deoxy-β-D-glucose or deoxy-glucose substituted by one or more groups such as acyl groups, or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring, for example, pyridyl such as 2-pyridyl or 4-pyridyl, pyrimidyl such as 2-pyrimidyl, imidazolyl such as 2-imidazolyl, or benzimidazolyl such as 2-benzimidazolyl; or an inorganic oxyacid or inorganic oxyacid derivative such as SO_3R or PO_3R_2 wherein R is hydrogen or alkyl.

More preferred complexes of formula (I) are:

2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),

2-hydroxyethanethiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),

2-aminoethanethiolate-(2,2':6',2"-terpyridine)platinum (II),

pyridine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
imidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
purine-6-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
purine-6-thiolate-bis[(4'-chloro-2,2'-6',2"-terpyridine)platinum (II)],
N,S-bis[(2,2':6',2"-terpyridine)platinum (II)] thioacetimine,

N,S-bis[(4'-chloro-2,2'-6',2"-terpyridine)platinum (II)] thioacetimine, diethylphosphorothioato(4'-chloro-2,2':6',2-terpyridine)platinum (II), succinylthiolatoplatinum (II) 2,2':6',2"-terpyridine, and 1-thio-β-D-glucose(2,2':6',2"-terpyridine)platinum (II).

The complexes of formula (I) may be negatively charged, neutral or positively charged. It will be appreciated that Y may be selected to obtain the desired overall charge. For example, when Y is PO_3^{2-} the overall charge on the compound of formula (I) is -1, when Y is $(PO_3R^1)^-$ wherein R^1 is for example C_1 to C_6 alkyl, the compound of formula (I) is neutral and when Y is $PO_3(R^1)_2$ wherein R is as defined above, the overall charge on the compound of formula (I) is +1. Compounds of formula (I) which are neutral overall may be able to pass through cell membranes more rapidly.

The present invention also includes the salts of the complexes of formula (I). When the complexes of formula (I) are positively or negatively charged a counterion is present. The counterions are physiologically tolerable counterions and are generally selected to obtain good water solubility. Counterions which may suitably be used include nitrate, sulphate, sulphonate, phosphate, pyrophosphate, phosphate esters and diesters, phosphonate, carbonate, carboxylate and any other non-toxic counterions which retains an appropriate level of solubility with the platinum (II) compound. Stable conjugates with anionic polymers or dendrimers may also be used and may be particularly appropriate for the delivery of the compounds of formula (I) to tumour cells because of the "enhanced cell permeability and retention effect" (EPR) of tumour cells. However, the (2,2':6',2"-terpyridine)platinum(II) complexes covalently react with human serum albumin and possibly other plasma proteins which can provide a natural and selective mechanism for delivery of these complexes into tumour cells. The plasma protein would be released by a thiol or more especially a selenocysteine dependent intracellular enzyme such as human thioredoxin reductase (see below).

The biological activity of the compounds of formula (I) may be affected by the leaving ability of the thiolate ligand which is linked to the pKa of the thiol Y-SH. Generally the pKa of the thiol is not more than 11. In one embodiment the pKa of

the thiol is greater than 6.

The present invention includes all possible isomers of the compounds of formula (I) and mixtures thereof, including diastereomeric mixtures and racemic mixtures, resulting from the possible combinations of (*R*) and (*S*) stereochemistry when stereogenic centres are present.

The compounds of formula (I) may be prepared by methods known in the art. For example, the compounds of formula (I) may be prepared from chloro(2,2':6',2"-terpyridine)platinum (II) chloride by treatment with a thiol Y-SH, in one instance the chloro(2,2':6',2"-terpyridine)platinum (II) chloride may be converted to a suitable salt before treatment with the thiol. The compounds of formula (I) may also be prepared from a complex formed from reacting a platinum complex of 1,5-cyclooctadiene with a 2,2':6',2"-terpyridine (see, for example, WO97/27202).

2-Hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II), in particular, shows a wide range of activities against protozoal parasites. It is effective against *Leishmania donovani, Trypanosoma cruzi* and *Trypanosoma brucei*. In addition 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II) has been shown to irreversibly inactivate the reduced form of human thioredoxin reductase and may therefore have potential as a therapeutic agent for rheumatoid arthritis. It has also been found to have anti-tumour activity against a range of human ovarian tumour cell lines.

Accordingly a human or animal may be treated by administering thereto a non-toxic and therapeutically effective amount of a compound which is a complex of formula (I). The condition of the human or animal may thereby be ameliorated. Protozoal infection, rheumatoid arthritis or tumours can thus be treated.

In another aspect the present invention provides use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an anti-protozoal, anti-rheumatoid arthritic or anti-tumour agent.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as active ingredient, in association with a pharmaceutically acceptable

carrier, excipient or other additive, if necessary.

The pharmaceutical composition containing a compound of formula (I) or salts thereof may be prepared in a conventional way by employing conventional non-toxic pharmaceutical carriers or diluents in a variety of dosage forms and ways of administration.

In particular, the compounds of formula (I) can be administered:

A) orally, for example, as tablets, troches, lozenges, aqueous or oily suspension, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such composition may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring and preserving agents in order to provide elegant and palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example maize starch or alginic acid; binding agents, for example maize starch, gelatin or acacia, and lubricating agents, for example magnesium stearate or stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such glyceryl monostearate or glyceryl distearate may be employed. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl cellulose, sodium

alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxyacetamol, or condensation products of ethylene oxide with partial esters derived from fatty acids and an hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol anhydrides, for example polyoxysorbitan monooleate.

The said aqueous suspension may also contain one or more preservatives, for example ethyl or n-propyl *p*–hydroxybenzoate, one or more colouring agents, one or more flavouring agents, one or more sweetening agents such as sucrose or saccharin.

An oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil, coconut oil or in a mineral oil such as liquid paraffin. The oily suspension may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation.

These compositions may be preserved by the addition of an antioxidant such as ascorbic acid. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions.

The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these.

Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy

bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, colouring and flavouring agents.

B) parenterally, either subcutaneously or intravenously or intramuscularly, or intrasternally, or by infusion techniques. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or olagenous suspensions.

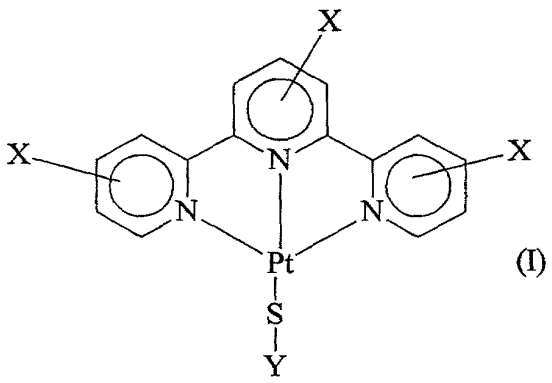
These suspensions may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose any bland fixed oils may be conventionally employed including synthetic mono or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables.

The daily dose varies according to the activity of the specific compound, the age, weight, and conditions of the subject to be treated, the type and the severity of the disease, and the frequency and route of administration. Typically the daily dose is from 0.1 to 50 mg per kg of body weight. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration may contain from 5 to 95% of the total composition. Dosage unit forms will generally contain between from 5 to 500 mg of the active compound.

In a further aspect the present invention provides a compound which is a

complex of formula (I)



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, alkylthio, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, with the proviso that the complex of formula (I) is not 2-hydroxyethanethiolate(2,2':6',2"-terpyridine)platinum (II) or 2-aminoethanethiolate(2,2':6',2"-terpyridine)platinum (II).

The Examples which follow further illustrate the present invention.

Examples

General procedures

Solvents (A.R. and h.p.l.c. grade) were purchased from Aldrich Chemical Company and Rathburn Chemicals. Diethylamine was dried over potassium hydroxide pellets, distilled from potassium hydroxide and stored under argon over potassium hydroxide pellets. Water refers to deionised water.

Melting points were determined on a Reichert heating stage and are uncorrected.

^{1}H n.m.r. spectra were recorded on a Varian Gemini 200MHz spectrometer or a Bruker AM 500 MHz spectrometer at 300K. Samples run in deuterochloroform ($CDCl_3$) were referenced to the solvent (7.26 ppm). Samples run in deuterium oxide (D_2O) were referenced to dioxane (3.75 ppm). Samples run in deuterated dimethylsulfoxide (DMSO) were referenced to the solvent (2.50 ppm). Chemical shifts are expressed in ppm. Abbreviations for multiplicity are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet; br d, broad doublet. Relative intensities are expressed as the number of protons such that "2H" denotes a relative intensity of two protons. ^{1}H n.m.r. spectra are expressed in order of chemical shift, multiplicity, coupling constant, relative intensity and assignment.

Flash chromatography was performed by using h.p.l.c. grade solvents and Merck silica gel 60 (230-400 mesh ASTM). Thin layer chromatography was performed on Merck precoated aluminium t.l.c. plates coated with silica gel 60F 254 (0.2 mm) and visualised by means of ultraviolet light.

Electrospray mass spectroscopy was carried out on a VG Biotech Bio-Q spectrometer using a dilute solution of the sample in methanol/water.

Antiparasitic Activity

SCREEN 1 -PROTOCOL 1

Leishmania donovani (strain MHOM/ET/67/L82) amastigotes, derived from the spleen of a golden hamster (Wright's strain) were used to infect mouse peritoneal macrophages from CD1 (Charles River Ltd., Margate, UK) mice at a parasite: macrophage ratio of 10:1. Infected macrophages were maintained in RPMI 1640 medium plus 10% heat inactivated fetal calf serum (hiFCS) (Harlan Sera-Lab.,

Crawley, UK) in 16-well Labtek chamber slides (Nunc Inc., IL, USA) at 37°C in 5% CO_2/air mixture. Infected cultures were exposed to test compounds in medium, in a three-fold dilution series from 30 μM with quadruplicate cultures at each concentration for 5 days, with medium + drug replaced once during the period. Sodium stilbogluconate (Glaxo Wellcome, UK) was included in the assays as the positive control and had an ED_{50} = 10.4 μg of Sb/mL (Mr of the drug is unknown) Activity was determined, after cultures had been methanol fixed and Giemsa stained, from the proportion of infected cells in treated and untreated cultures and dose response curves analysed by linear regression to obtain an ED_{50} value where possible.

Trypanosoma cruzi (strain MHOM/BR/00/Y) trypomastigotes derived from MDCK fibroblasts were used to infect mouse peritoneal macrophages from CD1 mice at a parasite: macrophage ratio of 5:1. Infected cells were maintained in RPMI 1640 medium plus 10% hiFCS in 16-well Labtek chamber slides at 37°C in 5% CO_2/air mixture. Infected cultures were exposed to test compounds in medium, in a three-fold dilution series from 30 μM with quadruplicate cultures at each concentration for 3 days. Nifurtimox (Bayer, Germany) was used as the positive control and had an ED_{50} in the range 2.2-4.4 μM. Activity was determined, after cultures had been methanol fixed and Giemsa stained, from the proportion of infected cells in treated and untreated cultures and dose response curves analysed by linear regression to obtain an ED_{50} value where possible.

Trypanosoma brucei brucei (strain S427) bloodstream trypomastigotes were cultured in HMI-18 medium containing 20% hiFCS at 37°C in 5% CO_2/air mixture. Trypomastigotes were exposed to test compounds in medium, in a three-fold drug dilution series from 30 μM with triplicate culures at each concentration for 72 hours. Pentamidine (Rhone Poulenc Rorer Ltd., Dagenham, UK) was used as the positive control and had an ED_{50} of 0.03-0.1μM. Drug activity was determined by using an MTT-based cytotoxicity assay and dose response curves analysed by linear regression to obtain an ED_{50} value where possible.

SCREEN 2 - PROTOCOL II

The assays follow those outlined in Screen 1- Protocol 1 but include a range of doses in a dilution series from 30μM. Dose response curves were analysed by linear regression and ED_{50} values determined. *T. brucei* numbers/ml are determined using a Coulter Counter.

Leishmania donovani: in vivo protocol.

Day 0 8 - 10 week old (18-20g) female BALB/C mice are infected with 2 x 10^7 *L. donovani* HU3 amastigotes, freshly harvested from the spleen of an infected Golden hamster. The inoculum is administered i.v. (lateral tail vein). The mice are randomly divided into groups of 5.

Day 7 1 mouse is sacrificed to check for patency of infection. An impression smear of the liver is made, Giemsa stained and examined. There should ideally be 1 amastigotes per nuclei (count 500 nuclei) This indicates a good, exponential infection. A group weight is measured and the average weight of mouse determined (should be approximately 20g). Commence dosing. Usual regimen is for 5 consecutive days.

Positive control mice are given Pentostam s.c. x 5 days - 45, 15 and 5 mgSbV/kg.

Day 14

All mice are weighed and necropsied. Livers and spleens are dissected and weighed. Impression smears are made, fixed (100% methanol) and Giemsa stained (10% Giemsa's for 45 minutes) for microscopical examination. The number of amastigotes per 500 nuclei is counted. This figure is then multiplied by the weight of the organ (mg). % inhibition compared with untreated control is calculated. In a dose-response experiment the ED_{50} is calculated by linear regression analysis (xlfit). The difference in group

weight can give an indication of toxicity but this is often obvious.

TBVV protocol: in vivo anti-trypanosomal (T.brucei spp.) assay

Day 1: 8-10 week old, female, BALB/C mice are infected with $5x10^4$ bsf (blood stream forms) of *T.b.rhodesiense* i.p. and randomly divided into groups of 5.

Day 2: All groups are weighed (average weight of mouse should be approximately 20g). Dosing commences. Compounds administered daily for 4 days. Positive control drug is Pentamidine 10mg/kg i.p. x 1 day.

Day 5 - 60:

Mice monitored daily until death. Untreated control groups die within 14 days post infection. Activity of compound is compared to this.

Inhibition of Trypanothione Reductase from Trypanosoma cruzi

The assay solution contains NADPH (100μM), trypanothione disulphide (100μM) and trypanothione reductase (3nM) in buffer at pH 7.5. The hydroxyethanethiolate complex (**1**) (40μM) leads to 95% irreversible inhibition of the enzyme within 20 min. If the NADPH is left out of the assay solution, (**1**) is a reversible competitive inhibitor with K_i= 60μM. The irreversibly inactivated enzyme (formed in the presence of NADPH) is stable to dialysis and thiols including glutathione, whereas the reversibly inhibited enzyme (in the absence of NADPH) is completely reversed on dialysis.

Human Glutathione Reductase

The hydroxyethanethiolate complex (**1**) (40μM) is not an irreversible inactivator of human glutathione reductase either in the presence or absence of NADPH.

Inhibition of Human Thioredoxin Reductase

The inhibition of human thioredoxin reductase was undertaken using the DTNB [5,5'-dithiobis-(2-nitrobenzoate)] assay (S. Gromer *et al.*, *J. Biol. Chem.*,

1998, *273*, 20096-20101).

The 2,2':6',2"-terpyridine Pt(II) complexes, (**1**), (**2**), (**3**), (**4**), (**6**), (7), (**8**), (**9**) and (**12**), at 20μM concentration, each irreversibly inhibited the enzyme completely within 10 min. in the presence of NADPH.

Materials

Human thioredoxin reductase (hTrxR) was purified from placenta as described by S. Gromer *et al.*, *J. Biol. Chem.*, **1998**, *273*, 20096-20101. Human glutathione reductase (hGR) was produced and isolated according to A. Nordhoff *et al.*, *Biochemistry*, **1993**, *32*, 4060-4066. Recombinant E.coli thioredoxin (EcTrx) with an (280nm of 13.6 mM-1cm-1 was produced as described in S.G. Mulrooney *et al.*, *Biochemistry*, **1994**, *33*, 3148-3154. The other substances for the enzymatic assays were purchased from Boehringer, Serva and Sigma, respectively. All reagents were of the highest purity available.

Enzyme assays

All assays were conducted at 25°C in a total assay volume of 1 ml.

Thioredoxin reductase activity: For determining TrxR activity two different assay systems were employed: In the DTNB reduction assay the enzyme was added to an assay mixture consisting of 100 mM potassium phosphate, 2 mM EDTA, pH 7.4 and 3 mM DTNB (100 mM stock solution in DMSO); after initiating the reaction with the addition of NADPH (200 µM final concentration), the increase in absorbance at 412 nm was monitored. 1 enzyme unit is defined as the NADPH-dependent production of 2 µmol 2-nitro-5-thiobenzoate ((412nm 13.6 mM-1cm-1) per min. In the Trx-assay the mixture contained 100 mM potassium phosphate, 2 mM EDTA, pH 7.4, 100 µM E.coli TrxS2 and 100 µM NADPH (ε340 nm 6.22 mM-1cm-1). The reaction was started with thioredoxin reductase (final concentration 4 nM TrxR subunits) and the decrease in absorbance at 340 nm was monitored during the linear phase. 1 enzyme unit is defined as the consumption of 1 µmol NADPH per min. For determining Km-values the assay mixtures contained varying concentrations of the respective substrates.

Glutathione reductase: The GR assay consisted of 47 mM potassium phosphate, 1 mM EDTA, 200 mM KCl, pH 6.9, and 100 µM NADPH; after the

addition of hGR the assay was started with 1 mM GSSG and the consumption of NADPH was monitored as the decrease in absorbance at 340 nm.

Protein concentrations were determined using the Bradford assay, M.M. Bradford, *Anal. Biochem.*, **1976**, *72*, 248-254, with bovine serum albumin as standard. In parallel, protein concentrations were determined on the basis of their specific absorbance at 280 nm and (for the flavoenzymes) at 463 nm (ε 280 nm = 11.3 mM-1cm-1).

Antitumour Activity

The thiolato-2,2':6',2"-terpyridine Pt(II) complexes (**1**) and (**4**) to (**9**) and also imidazole-2-thiolate-bis[(2,2':6',2"-terpyridine) platinum(II)] bisnitrate (**13, A_{21}.2N**), benzimidazole-2-thiolate-bis[(2,2':6',2"-terpyridine) platinum(II)] bisnitrate (**14,A_{22}.2N**), pyridine-4-thiolate-(2,2':6',2"-terpyridine) platinum(II) bisnitrate (**15,A_{23}.2N**), and pyrimidine-2-thiolate-(2,2':6',2"-terpyridine) platinum(II) bisnitrate (**16,A_{24}.2N**) were evaluated for *in vitro* cytotoxicity against five human ovarian carcinoma cell lines which included two selected for resistance to cisplatin ($CHIcis^R$ and $A2780cis^R$) and one for resistance to doxorubicin ($CHIdox^R$). The compounds were exposed to cells for 96 h and growth inhibition assessed using the sulforhodamine B protein staining assay. The IC_{50} values (in μM) are shown in Table 5. Cisplatin and carboplatin are included for comparison.

Cell culture conditions

Primary glioblastomas and HNSCC (head and neck squamous cell carcinoma) cells were cultured by dissecting tissue in small pieces of about 1mm and transferring in 75cm^2 plastic tissue culture flasks (Falcon, Becton Dickinson, Heidelberg, Germany). Cells were cultured routinely in RPMI 1640 supplemented with 60% fetal calf serum and antibiotics at 37°C, 5% CO_2, and 95% air in a humidified incubator with medium changes twice a week. After reaching confluency cells were harvested by a brief incubation with trypsin/EDTA solution (Viralex, PAA, Linz, Austria) and seeded into a fresh 75 cm^2 plastic tissue culture flask. Tumor cells were characterized for their astrocytic or epithelial origin by the immunhistochemical detection of tissue specific markers like GFAP for glioma cells (NCH37, NHC82 and NHC89) and a pannel of different cytokeratins for head and

neck squamous carcinoma cells (HCSCC cells) (HNO97 and HNO199). Only cell cultures showing a homogeneous staining for the respective marker were used in this study.

Proliferation assay

The assay was performed as described in U. Maurer *et al.*, *European J. Cancer*, **1999**, *35*, 544, with the BrdU Labelling and Detection Kit III by Roche Diagnostics, Mannheim. Cells were seeded in 8 replicas in 96-well plates in RPMI 1640 supplemented with 10% FCS and antibiotics (cell densities: 7 x 103 cells). After 24 hrs the synthetic compounds I_{23}.N (**6**) and A_{26}.3N (**9**) were added in different concentrations (1 µM, 5 µM, 10 µM and 20 µM) following two application protocols: either a single addition on the first day of the 67 hrs incubation time or 3 repeated additions in 24 hrs intervals again with a total incubation time of 67 hrs. 48 hrs after first addition of the compounds BrdU was added to the wells for 19 hrs at a final concentration of 10 mM. The assay was processed according to manufacturers instructions. Optical density was determined and the mean value of the control samples containing no synthetic compound was arbitrarily set to 100%. Values are means of at least 2 independent experiments (8 replicas each) with SD as average deviation of the mean value.

Chemosensitivity testing in vitro (see Table 9)

Adherent cell lines: Cells which strongly adhere to tissue culture plastics are initially trypsinised from stock culture flasks and between 1 and 2 x 10^3 cells are placed into each well of a 96 well plate (U shaped wells) with each well containing a final volume of medium of 200 μl. Following an overnight incubation at 37°C in an atmosphere containing 5% CO_2 / 95 % air, all medium is removed and replaced with medium containing drug. Cells are exposed to a range of drug concentrations (8 wells per drug exposure). Each plate contains a blank (medium only / no cells) and a control (drug vehicle only). For continuous drug exposures, the plates are incubated for 5 days at 37 °C prior to assessing cell survival. For timed exposures, drug solutions are removed and the cells are washed twice with Hanks Balanced Salt Solution (HBSS, 200 μl per well per wash). Following washing, 200 μl of medium is added to each well and the cells incubated for 5 days at 37 °C.

Suspension cell cultures

A) Timed exposures. Cells which do not attach to plastic culture plates are exposed to a range of drug solutions in universal tubes containing 5 ml of medium + drug. Following drug exposure, cells are centrifuged (1000 x g for 5 mins) and the pellet resuspended in HBSS. Following a further washing step, cells are resuspended in growth medium, counted using a haemocytometer and between 1 and 2 x 10^3 cells plated into each well of a 96 well plate as described above (ie 8 wells per drug exposure). Cells are then incubated for 5 days prior to chemosensitivity assessment.

B) Continuous exposure. Between 1 and 2 x 10^3 cells are plated into each well of a 96 well plate (180 μl cell suspension per well). Drug solutions at 10 times the desired final concentration are added to each well (20 μl drug per well, 8 wells per drug concentration), and the solutions mixed by gentle tapping of the plate. Plates are then incubated for 5 days.

Chemosensitivity testing using the MTT assay

Following either a 5 day post drug exposure recovery period or a 5 day continuous exposure to drugs, 20 μl of MTT (5 mg ml^{-1}) is added to each well of the 96 well plate. Following a further 4 hour incubation at 37°C, medium is completely removed from each well (this applies only to adherent cell lines) and the formazan crystals dissolved in 150 μl DMSO per well. For suspension cultures, 200 μl of medium plus MTT is removed from each well (taking care not to disturb the formazan crystals) prior to the addition of 150 μl DMSO per well. Once the formazan has dissolved, the solution is mixed (using a spatula) and the absorbance of the resulting solution determined at 550 nm using a multi-well spectrophotometer. Cell survival is calculated from the mean absorbance of the treated plates (mean of 8 wells) divided by the mean absorbance of the control (mean of 8 wells) and the final result is expressed as percent cell survival taking the absorbance of the control cultures to be 100 % survival.

Standard Operating Procedures

Chemosensitivity testing in vitro:

Adherent cell lines:

Trypsinise from stock cultures

1 - 2 x 10^3 cells per well of a 96 well plate

(U shaped wells)

200 μl. Total volume

Continuous drug exposures, 5 days at 37 °C

Timed exposures, drug solutions are removed and the cells are washed twice with Hanks Balanced Salt Solution (HBSS, 200 μl per well per wash). Following washing, 200 μl of medium is added to each well and the cells incubated for 5 days at 37 °C.

Suspension cell cultures:

A) Timed exposures.

Cells exposed to a range of drug solutions in universal tubes containing 5 ml of medium + drug.

Cells are centrifuged (1000 x g for 5 mins)

Resuspended in HBSS. Washed twice Resuspended in growth medium

1 - 2 x 10^3 cells plated into each well of a 96 well plate (8 wells per drug exposure). Cells are then incubated for 5 days prior to chemosensitivity assessment.

B) Continuous exposure.

1 - 2 x 10^3 cells per well of a 96 well plate (180 μl cell suspension per well). Drug solutions at 10 times the desired final concentration are added to each well (20 μl drug per well, 8 wells per drug concentration), and the solutions mixed by gentle tapping of the plate. Plates are then incubated for 5 days.

Synthesis of 2,2':6',2"-Terpyridine Platinum (II) Complexes

By way of example the synthesis and characterisation of the several thiolate-2,2':6',2"-terpyridine platinum (II)] complexes are provided. The platination of 2,2':6',2"-terpyridine and 4'-chloro-2,2':6',2"-terpyridine was achieved as previously described (WO97/27202 and *J.Chem. Res.*, **1996**, 386-387).

2-Hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate (1, A_{het}.N) was prepared by the following general method which is more effective and reliable than the literature method. (K. Jennette *et al.*, *Proc. Natl. Acad. Sci. USA*, **1974**, *71*, 3839-3843).

Silver nitrate (35.7mg, 0.21mmol) was dissolved in aqueous acetone (4: 1

acetone: water, 0.5ml) and added to a suspension of diiodo-1,5-cylooctadienyl platinum (I) (55.7mg, 0.1mmol) in aqueous acetone (0.75ml). The mixture was vigourously shaken until the dark yellow colour had subsided then the precipitated silver salt isolated by centrifugation and discarded. The supernatant containing the active platinum species was added to a suspension of 2,2':6',2"-terpyridine (0.08mmol, 18.7mg) in acetonitrile (0.25ml). After standing for *ca.* 5 min. the yellow precipitate formed was isolated by centrifugation, washed with ether: acetonitrile (3: 1, 3x1.5ml) then redissolved in demineralised water (1ml). To this solution was added mercaptoethanol (7.54µl = 8.6mg, 0.11mmol). After standing for 1 hour the product was isolated by precipitation from excess acetone: ether (5: 3, 40ml), washed with acetone: ether then ether alone and dried in a vacuum dessicator.

The product was a brick-red powdery solid (35.9mg, 79.1%).

Electrospray mass spectrum and 500MHz proton nmr precisely matched that from material made *via* the literature method from $[Pt(Terpy)Cl]^+.Cl^-$.

2-Hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine) platinum (II) nitrate (2, I_{het}.N)

4'-Chloro-2,2':6',2"-terpyridine is commercially available from Aldrich Chemical Co., UK or Lancaster, UK. The preparation of the title compound was by the general method given above.

The product was a dark red powdery solid (23.5mg, 48.8%).

m/z (ESI+, *ex.* MeOH: H_2O): 540 (M^+); δ_H (500MHz, D_2O, referenced to dioxan (3.75ppm)/ ppm: 9.03 (2H, d, *J* 5.3 Hz, broadened, H6,6"), 8.37 (2H, s, H3'/5'), 8.34 (2H, td, *J* 7.9, 1.3Hz, H4,4"), 8.14 (2H, d, *J* 7.8Hz, H3,3"), 7.79 (2H, m, H5,5"), 3.67 (2H, t, *J* 6.9Hz, OCH_2CH_2S), 2.56 (2H, t, *J* 6.8Hz, OCH_2CH_2S).

2-Hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine) platinum (II) nitrate (3, Y_{het}.N)

4'-Ethoxy-2,2':6',2"-terpyridine was prepared in excellent yield by ethanolysis of 4'-chloro-2.2':6'.2"-terpyridine activated by $FeCl_2.4H_2O$ or by reaction with sodium ethoxide without activation, m.p. 85-86°C. TLC (alumina, petroleum ether 40-60°C / EtOAc 3 / 1) : $R_f = 0.59$. δ_H (200 MHz, $CDCl_3$) : 8.70 (*d*, $^3J(6,5) = 4.1$, 2H, H-C(6), H-C(6")); 8.63 (*d*, $^3J(3,4)=8.1$, 2H, H-C(3) , H-C(3")); 8.02 (*s*, 2H, H-

C(3'), H-C(5')); 7.86 (*dt*, $^4J(4,6) = 1.8$, $^3J(4,3) = {}^3J(4,5) = 7.3$, 2H, H-C(4), H-C(4")); 7.34 (*ddd*, $^4J(5,3) = 1.2$, $^3J(5,6) = 4.8$, $^3J(5,4) = 7.5$, 2H, H-C(5), H-C(5")); 4.32 (*q*, 2H, $^3J_{vic} = 7.1$, 2H, $\underline{H}_2$-COterpy); 1.50 (*t*, $^3J_{vic} = 6.9$, $\underline{H}_3$-CCH_2). m/z (ESI) : 278 (MH^+).

4'-Ethoxy-2,2':6',2"-terpyridine (0.08mmol, 22.2mg) was used in the general method described above to give the title product as a dark red powdery solid (26.9mg, 55.0%).

m/z (ESI+, *ex.* MeOH: H_2O): 549 (M^+); δ_H (500MHz, D_2O, referenced to dioxan (3.75ppm)/ ppm: 8.96 (2H, d, *J* 5.1 Hz, broadened, H6,6"), 8.23 (2H, t, *J* 7.3Hz, H4,4"), 8.03 (2H, d, *J* 7.9Hz, H3,3"), 7.69 (2H, m, H5,5"), 7.60 (2H, s, H3'/5'), 4.30 (2H, q, J 7.0Hz, OCH_2CH_3), 3.68 (2H, t, *J* 6.9Hz, OCH_2CH_2S), 2.53 (2H, s, broadened, OCH_2CH_2S), 1.53 (3H, t, J 6.5Hz, OCH_2CH_3).

Pyridine-4-thiolate(2,2':6',2"-terpyridine)platinum(II) nitrate (A_{23}.N)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 4-mercaptopyridine (13.3 mg, 0.12 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 4-mercaptopyridine (2,2':6',2"-terpyridine)platinum(II) nitrate (40 mg, 83%) as a orange solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.75, d, *J*=5.4 Hz, 2H, H6, H6"; 8.48, t, *J*=8.1 Hz, 1H, H4'; 8.36-8.29, m, 4H, H4, H4", H3', H5'; 8.24, d, *J*=7.8 Hz, 2H, H3, H3"; 7.99, AA'BB'm, 4H, H2"', H3"', H5"', H6"'; 7.63, m, 2H, H5, H5".

Pyridine-4-thiolate(4'-chloro-2,2':6',2''-terpyridine)platinum(II) nitrate (6, I_{23}.N)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2''-terpyridine (21.4 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 4-mercaptopyridine (13.3 mg, 0.12 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 4-mercaptopyridine (4'-chloro-2,2':6',2''-terpyridine)platinum(II) nitrate (45 mg, 89%) as a orange-brown solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.83, d, J=5.5 Hz, 2H, H6, H6''; 8.55, s, 2H, H3', H5'; 8.39, apparent t, J=7.9 Hz, 2H, H4, H4''; 8.28, d, J=7.7 Hz, 2H, H3, H3''; 8.00, AA'BB'm, 4H, H2''', H3''', H5''', H6'''; 7.71, m, 2H, H5, H5''.

Pyridine-2-thiolate(2,2':6',2''-terpyridine)platinum(II) nitrate (A_{25}.N)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2''-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyridine (15 mg, 0.13 mmol)

in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyridine (2,2':6',2"-terpyridine)platinum(II) nitrate (42 mg, 88%) as a yellow solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml).

Pyridine-2-thiolate(4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate ($\mathbf{8, I_{25}.N}$)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyridine (15 mg, 0.13 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyridine (4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate (42 mg, 82%) as a yellow solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml).

Imidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate ($\mathbf{13, A_{21}.2N}$)

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine

(33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptoimidazole (6.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptoimidazole bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (57 mg, 88%) as a crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.72, d, J=5.5 Hz, 2H, H6, H6"; 8.44, t, J=8.2 Hz, 2H, 2xH4'; 8.30-8.27, m, 4H, 2xH4, 2xH4"; 8.10, d, J=8.2 Hz, 2H, H3', H5'; 8.09, d, J=8.2 Hz, 2H, H3', H5'; 8.05, d, J=8.0 Hz, 2H, H3, H3"; 8.02, d, J=7.9 Hz, 2H, H3, H3"; 7.89, d, J=5.5 Hz, 2H, H6, H6"; 7.54-7.48, m, 5H, 2xH5, 2xH5", either H_x or H_y; 7.34, d, J=1.8 Hz, 1H, either H_x or H_y.

Imidazole-2-thiolate-bis[(4'chloro-2,2':6',2"-terpyridine)platinum(II)] dinitrate (4, I_{21}.2N)

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (38.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptoimidazole (6.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptoimidazole bis[(4'-chloro-2,2':6',2"-terpyridine)platinum(II)] dinitrate (66 mg, 96%) as a dark

purple solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.78, d, *J*=5.6 Hz, 2H, H6, H6"; 8.47, s, 2H, H3', H5'; 8.46, s, 2H, H3', H5'; 8.34-8.27, m, 4H, 2xH4, 2xH4"; 8.08, d, *J*=8.3 Hz, 2H, H3, H3"; 8.05, d, *J*=8.2 Hz, 2H, H3, H3"; 7.94, d, *J*=5.6 Hz, 2H, H6, H6"; 7.60-7.54, m, 4H, 2xH5, 2xH5"; 7.51, apparent broad s, 1H, either H_x or H_y; 7.34, apparent broad s, 1H, either H_x or H_y.

Benzimidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (14, A_{22}.2N)

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptobenzimidazole (9.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptobenzimidazole bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (64 mg, 94%) as a crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.86, d, *J*=4.9 Hz, 2H, H6, H6"; 8.49, t, *J*=8.2 Hz, 1H, H4'; 8.47, t, *J*=8.2 Hz, 1H, H4'; 8.27-8.22, m, 4H, 2xH4, 2xH4"; 8.15, d, *J*=8.2 Hz, 2H, H3', H5'; 8.14, d, *J*=8.2 Hz, 2H, H3', H5'; 8.08, d, *J*=7.8 Hz, 2H, H3, H3"; 8.04, d, *J*=7.8 Hz, 2H, H3, H3"; 7.77, d, *J*=4.8 Hz, 2H, H6, H6"; 7.71, d, *J*=8.2 Hz, 1H, either Hz or Hw; 7.67, d, *J*=8.2 Hz, 1H, either Hz or Hw; 7.49, m, 2H, H5, H5"; 7.45, t, *J*=7.8 Hz, 1H, either Hx or Hy; 7.36, m, 2H, H5, H5"; 7.29, t, *J*=8.1 Hz, 1H, either Hx or Hy.

Benzimidazole-2-thiolate-bis[(4'-chloro-2,2':6',2''-terpyridine)platinum(II)] dinitrate (5, I_{22}.2N)

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2''-terpyridine (38.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptobenzimidazole (9.01 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptobenzimidazole bis[(4'-chloro-2,2':6',2''-terpyridine)platinum(II)] dinitrate (55 mg, 77%) as a yellow-brown solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.95, d, *J*=4.8 Hz, 2H, H6, H6''; 8.53, s, 2H, H3', H5'; 8.51, s, 2H, H3', H5'; 8.31-8.25, m, 4H, 2xH4, 2xH4''; 8.12, d, *J*=7.8 Hz, 2H, H3, H3''; 8.07, d, *J*=7.3 Hz, 2H, H3, H3''; 7.83, d, *J*=4.5 Hz, 2H, H6, H6''; 7.71, d, *J*=8.2 Hz, 1H, either Hz or Hw; 7.67, d, *J*=8.1 Hz, 1H, either Hz or Hw; 7.56, m, 2H, H5, H5''; 7.46, t, *J*=7.6 Hz, 1H, either Hx or Hy; 7.43, m, 2H, H5, H5''; 7.30, t, *J*=7.6 Hz, 1H, either Hx or Hy.

Pyrimidine-2-thiolate (2,2':6',2''-terpyridine)platinum(II) nitrate (A_{24}.N)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2''-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and

discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyrimidine (8.9 mg, 0.080 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyrimidine (2,2':6',2"-terpyridine)platinum(II) nitrate (43 mg, 90%) as a dark crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.75, d, J=5.5 Hz, 2H, H6, H6"; 8.42, t, J=8.1 Hz, 1H, H4'; 8.31-8.19, m, 8H, H3, H3", H4, H4", H3', H5', Hx, Hz; 7.60, apparent t, J=7.2 Hz, 2H, H5, H5"; 7.01, t, J=5.0 Hz, 1H, Hy.

Pyrimidine-2-thiolate (4'-chloro-2,2':6',2''-terpyridine)platinum(II) nitrate (7, I_{24}.N)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.3 mg, 0.100 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (21.4 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptopyrimidine (8.9 mg, 0.080 mmol) in methanol/water (1:1, 1.0 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 2-mercaptopyrimidine (4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate (35.2 mg, 69%) as a dark purple solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 8.81, d, J=4.8 Hz, 2H, H6, H6"; 8.49, s, 2H, H3', H5'; 8.36,

apparent t, *J*=7.9 Hz, 2H, H4, H4"; 8.25, d, *J*=5.0 Hz, 2H, Hx, Hz; 8.23, d, *J*=7.8 Hz, 2H, H3, H3"; 7.68, apparent t, *J*=6.7 Hz, 2H, H5, H5"; 7.03, t, *J*=5.0 Hz, 1H, Hy.

Purine-6-thiolate bis[(2,2':6',2''-terpyridine)platinum(II)] dinitrate

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A suspension of 6-mercaptopurine (10.2 mg, 0.060 mmol) in water (6 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 6-mercaptopurine bis[(2,2':6',2"-terpyridine)platinum(II)] dinitrate (57 mg, 84%) as a purple-brown solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 9.31, s, 1H, Hy; 8.78, s, 1H, Hx; 8.73, d, *J*=5.1 Hz, 2H, H6, H6"; 8.51, t, *J*=8.1 Hz, 1H, H4'; 8.48, t, *J*=8.2 Hz, 1H, H4'; 8.32-8.25, m, 4H, 2xH4, 2xH4"; 8.19, d, *J*=8.2 Hz, 2H, H3', H5'; 8.14, d, *J*=8.2 Hz, 2H, H3', H5'; 8.11-8.07, m, 4H, 2xH3, 2xH3"; 7.89, d, *J*=4.9 Hz, 2H, H6, H6"; 7.49-7.46, m, 4H, 2xH5, 2xH5".

Purine-6-thiolate bis[(4'-chloro-2,2':6',2''-terpyridine)platinum(II)] dinitrate

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4'-chloro-2,2':6',2"-terpyridine (38.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The

supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 2-mercaptobenzimidazole (10.2 mg, 0.060 mmol) in water (3 ml) was added. The mixture was vortexed and then sonicated for 1.5 h. The mixture was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 6-mercaptopurine bis[(4'-chloro-2,2':6',2"-terpyridine)platinum(II)] dinitrate (67.1 mg, 93%) as a crimson solid. The product was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz, D_2O}: ∂ 9.31, s, 1H, Hy; 8.79-8.77, m, 3H, Hx, H6, H6"; 8.56, s, 2H, H3', H5'; 8.52, s, 2H, H3', H5'; 8.35-8.29, m, 4H, 2xH4, 2xH4"; 8.13-8.08, m, 4H, 2xH3, 2xH3"; 7.94, d, *J*=5.0 Hz, 2H, H6, H6"; 7.57-7.48, m, 4H, 2xH5, 2xH5".

1-Thio-β-D-glucose (2,2':6',2"-terpyridine)platinum(II) nitrate (12, A_{tgl}-N)

A solution of silver nitrate (37.0 mg, 0.218mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (55.0 mg, 0.102 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (18.7 mg, 0.080 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x1.5 ml) and then dissolved in water (0.75 ml). A solution of 1-thio-β-D-glucose (15.3 mg, 0.070 mmol) in water (2 ml) was added. The mixture was vortexed and sonicated for 45 min and then added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried to yield 1-thio-β-D-glucose (2,2':6',2"-terpyridine)platinum(II) nitrate (38 mg, 79%) as a dark purple solid. The product was purified by re-precipitation from methanol/ether/acetone (1:4:5, 20 ml). ^{1}H n.m.r. {500 MHz, D_2O}: ∂ 9.11, br d, *J* 3.4 Hz, 2H, H6, H6"; 8.32, t, *J* 8.1 Hz, 1H, H4'; 8.25, m, 2H, H4, H4"; 8.12, d, *J* 8.1 Hz, 2H, H3', H5'; 8.07, d, *J* 7.9 Hz, 2H, H3, H3"; 7.68, m, 2H, H5, H5"; 4.42, d, *J* 8.7 Hz, 1H, Ha; 3.71, d, *J* 11.6 Hz, 1H, either Hc or Hd; 3.51, dd, *J* 5.5, 11.9 Hz, 1H,

either Hc or Hd; 3.35-3.23, m, 4H, Hx, Hy, Hb, He. ESMS (1:1 MeOH:H_2O, CV=30V): *m/z* 623.5 (M^+, 97%).

N,S-Bis[(2,2':6',2"-terpyridine)platinum (II)] thioacetimine trinitrate (9, A_{26}.3N)

A solution of silver nitrate (64.6 mg, 0.38 mmol) in acetone/water (4:1, 0.6 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (99.6 mg, 0.18 mmol) in acetone/water (4:1, 0.6 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 2,2':6',2"-terpyridine (33.6 mg, 0.144 mmol) in acetonitrile (0.3 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet was washed with acetonitrile/ether (1:3, 2x2.0 ml), dissolved in water (0.75 ml). A solution of thioacetamide (5.41 mg, 0.070 mmol) in water (6 ml) was then added. The mixture was vortexed and then sonicated for 1 h. The mixture was added dropwise to ether/acetone (1:1, 25 ml) to precipitate the complex and yielded *N,S*-bis(2,2':6',2"-terpyridine)platinum(II) thioacetimine trinitrate as a dark purple-brown solid (52 mg, 67%). The solid was washed with ether/acetone (1:1, 4x20 ml) and then dried. The solid was purified by dissolving the solid in hot methanol/water (1:1) and re-precipitating from ether/acetone (1:1, 25 ml). ^{1}H n.m.r. {400 MHz D_2O}:δ 8.77, d, *J*=5.5 Hz, 2H, H6, H6"; 8.42, t, *J*=8.2 Hz, 1H, H4': 8.38, t, *J*=8.2 Hz, 1H, H4'; 8.30, d, *J*=5.1 Hz, 2H, H6, H6"; 8.28-8.20, m, 4H, 2xH4, 2xH4"; 8.10, d, *J*=8.2 Hz, 2H, H3', H5', 8.05, d, *J*=8.2 Hz, 2H, H3', H5'; 8.01, d, *J*=7.7, Hz, 2H, H3, H3"; 8.00, d, *J*=7.7 Hz, 2H, H3, H3"; 7.58-7.52, m, 4H, 2xH5, 2xH5"; 2.87, s, 3H, CH_3.^{1}H n.m.r. {500 MHz, DMSO}: ∂ 10.60, s, 1H, NH; 8.82, d, *J*=5.6 Hz, 2H, H6, H6"; 8.55, t, *J*=8.1 Hz, 1H, H4',; 8.52, t, *J*-8.1 Hz, 1H, H4'; 8.44, d, *J*=5.5 Hz, 2H, H6, H6"; 8.41, d, *J*=8.1 Hz, 2H, H3', H5'; 8.37, d, *J*=8.1 Hz, 2H, H3', H5'; 8.34-8.32, m, 8H, 2xH3, 2xH3", 2xH4, 2xH4"; 7.70-7.64, m, 4H, 2xH5, 2xH5"; 2.95, s, 3H, CH_3.ESI (1:1 MeOH:H_2O, CV=20 V): *m/z* 310.1 (M^{3+}, 100%), 444.1 {[Pt(terpy)-S-Pt(terpy)]$^{2+}$, 69%}.

N,S-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)] thioacetamide trinitrate (**17, I_{26}.3N**) may be prepared in an analogous manner.

Diethylphosphorothioato(4'-chloro-2,2':6',2"-terpyridine)platinum(II) nitrate (10, I_{27}.N)

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpydine)platinum (II) nitrate (**1**, A_{het}.N) but using 4'-chloro-2,2':6',2"-terpyridine and triethylammonium diethylphosphorothioate on a 0.1 mmol scale. Recrystallisation from acetone and ether afforded the product as a yellow solid (47 mg, 68%). mp >230°C. δ_{1H} (250MHz; D_2O) 8.69 (2H, d, *J*=5Hz, H6,6"); 8.28 (2H, s, H3',5'); 8.21 (2H, t, *J*=8Hz, H4,4"); 8.03 (2H, d, *J*=8Hz, H3,3"); 7.62 (2H, t, *J*=5Hz, H5,5"); 3.80 (4H, dq, *J*=7.7Hz, CH_2); 0.86 (6H, t, *J*=7Hz, CH_3). δ31p (101MHz, d_6 DMSO) 31.93 ($^{195}Pt_{sat}$.at 31.50 and 32.27, *J* 195_{Pt}-31_P=88Hz). m/z (ESI+)=631 (M^+).

Succinylthiolatoplatinum (II) 2,2';6',2"-terpyridine nitrate (11, A_{MS} N)

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II) nitrate (**1**, A_{het}.N) except that instead of adding mercaptoethanol, an acidified solution of mercaptosuccinic acid (20mg, 0.13mmol) in water (1.25ml, acidified by addition of HNO_3, to pH < 1) was added and the mixture heated to 80°C until the solid was completely dissolved. Slow cooling of the solution afforded the title compound as bright red crystals which were isolated by filtration and washed with strongly acidified water (27.9mg, 55%). mp > 230°C. δ_{1H} (500MHz; D_2O): 9.37 (2H, d, *J*=6.0Hz, H6,6"); 8.69 (2H, d *J*=8.0Hz, H3,3"); 8.62 (3H, m, H3',5' + H4'); 8.50 (2H, t, *J*=8.0Hz, H4, 4"); 7.97 (2H, m, H5,5"); 3.45 (1H, dd, *J*=9.0, 5.5Hz, Hα); 2.86 (1H, dd, *J*=16.5, 10.0Hz, Hβ); 2.75 (1H, dd, *J*=16.5, 5.5Hz, Hβ). m/z (ESI+)=577.1 ($[M]^+$).

4'-n-Butyloxy-2,2':6',2"-terpyridine

NaH (240 mg, 6 mmol) and 1-butanol (800 mg, 10 mmol) in DMF (10ml) were stirred for 30 min at room temperature. 4'-chloro-2,2':6',2"-terpyridine (534 mg, 2 mmol) was added and this mixture was stirred overnight at 80 °C under argon. On adding an equal amount of water to the DMF the product precipitated and was filtered off and washed with water. The product is recrystalised from EtOH (0.587 g, 95%). (Found: C, 73.9; H, 6.5; N, 12.2. Calc. for $C_{19}H_{20}N_3O$: C, 74.5; H, 6.5; N, 13.7%). ^1H NMR ($CDCl_3$): δ = 1.1 [t, 3 H, J = 7 Hz, CH_3], 1.61 [sextet, 2 H, J = 7

Hz, CH_2CH_3], 1.95 [q, 2 H, J = 6 Hz, CH_2CH_2O], 4.31 [t, 2 H, J = 7 Hz, CH_2O], 7.40 [ddd, 2 H, J = 7.5, 5.0, 1.0 Hz, H5,5''], 7.92 [dt, 2 H, J = 8.0, 7.6, 1.8 Hz, H4,4''], 8.08 [s, 2 H, H3',5'], 8.69 [ddd, 2 H, J = 8.0, 2.0, 1.0 Hz, H3,3''], 8.79 [ddd, 2 H, J = 5.0, 2.0, 1.0 Hz, H6,6''] DCI-MS; *m/z* (%): 306 (100) [MH^+] $C_{19}H_{19}N_3O$ (305.0).

2-Hydroxyethanethiolate-(4'-n-butyloxy-2,2':6',2''-terpyridine) platinum(II) nitrate

$AgNO_3$ (71.4 mg, 0.42 mmol) in aq. acetone (80% acetone, 0.25 ml) was added to a suspension of $Pt(COD)I_2$ (111.4 mg, 0.2 mmol) in aq. acetone (0.75 ml). AgI was removed by centrifugation. The supernatant was added to a suspension of ligand 4'-n-butyloxy-2,2':6',2''-terpyridine (58.1 mg, 0.19 mmol) in MeCN/Dioxane (1 :1, 10 ml). After 5 min the product precipitates. Ether (30 ml) was added, and the suspension vortexed and centrifuged and the supernatant discarded. The solid was washed with ether, taken up in DMF (5 ml) and mercaptoethanol (40 µl, 0,40 mmol) added. The solid is precipitated with ether, isolated by centrifugation, washed with ether and dried *in vacuo*. Yield (100 mg, 82%). (Found: C, 39.8; H, 4.1; N, 8.7. Calc. for $C_{21}H_{24}SN_4O_5Pt$: C, 39.4; H, 3.8; N, 8.8%). ^1H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.55 [m, 2 H, (CH_2CH_3)], 1.97 [m, 2 H, (CH_2CH_2O)], 2.40 [t, 2 H, J = 7 Hz, SCH_2], 3.50 [t, 2 H, J = 7 Hz, $HOCH_2$], 4.38 [t, 2 H, J = 7 Hz, CH_2O], 4.81 [s, 1 H, *OH*], 7.82 [t, 2 H, J = 7.0 Hz, H5,5''], 8.21 [s, 2 H, H3',5'], 8.35 [t, 2 H, J = 7.0 Hz, H4,4''], 8.50 [d, 2 H, J = 8.0 Hz, H3,3''], 9.28 [d, 2 H, J = 6.0 Hz, H6,6''].

4'-n-Hexyloxy-2,2':6',2''-terpyridine

The title compound was prepared by a method analogous to 4'-n-butyloxy-2,2':6',2''-terpyridine using 1-hexanol in place of 1-butanol. Yield (0.744 g, 100%). (Found: C, 75.7; H, 7.7; N, 12.7. Calc. for $C_{21}H_{23}N_3O$: C, 75.7; H, 7.7; N, 12.7%). ^1H NMR ($CDCl_3$): δ = 1.00 [t, 3 H, J = 7 Hz, CH_3], 1.50 [m, 6 H, ($CH_2CH_2CH_2$ CH_3)], 1.95 [q, 2 H, (CH_2CH_2O)], 4.37[t, 2 H, J = 7 Hz, CH_2O], 7.65 [ddd, 2 H, J = 7.5, 5.0, 1.0 Hz, H5,5''], 8.10 [s, 2 H, H3',5'], 8.19 [dt, 2 H, J = 8.0, 7.6, 1.8 Hz, H4,4''], 8.79 [ddd, 2 H, J = 8.0, 2.0, 1.0 Hz, H3,3''], 9.05 [ddd, 2 H, J = 5.0, 2.0, 1.0 Hz, H6,6''].

DCI-MS; *m/z* (%): 334 (100) [MH^+] $C_{21}H_{23}N_3O$ (333.0).

2-Hydroxyethanethiolate-(4'-n-hexyloxy-2,2':6',2''-terpyridine) platinum(II) nitrate

The title complex was prepared by a method of analogous to (**1,A_{het}.N**). Yield (105 mg, 83%) (Found: C, 41.5; H, 4.4; N, 8.4. Calc. for $C_{23}H_{28}SN_4O_5Pt$: C, 41.4; H, 4.2; N, 8.4%). ^{1}H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.50 [m, 6 H, ($CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 2.42 [t, 2 H, J = 7 Hz, SCH_2], 3.58 [t, 2 H, J = 7 Hz, $HOCH_2$], 4.34 [t, 2 H, J = 7 Hz, CH_2O], 4.69 [s, 1 H, O*H*], 7.90 [t, 2 H, J = 7.0 Hz, H5,5''], 8.22 [s, 2 H, H3',5'], 8.38 [t, 2 H, J = 7.0 Hz, H4,4''], 8.59 [d, 2 H, J = 8.0 Hz, H3,3''], 9.28 [d, 2 H, J = 6.0 Hz, H6,6''].

4'-n-octyloxy-2,2':6',2''-terpyridine

The title compound was prepared by a method analogous to 4'-n-butyloxy-2,2':6',2''-terpyridine. Yield (0.474 g, 66%). (Found: C, 76.4; H, 7.4; N, 11.6. Calc. for $C_{23}H_{27}N_3O$: C, 76.5; H, 7.5; N, 11.6%). ^{1}H NMR ($CDCl_3$): δ = 0.98 [t, 3 H, J = 7 Hz, CH_3], 1.50 [m, 10 H, $CH_2CH_2CH_2CH_2CH_2$ CH_3], 1.95 [q, 2 H, J = 6 Hz, CH_2CH_2O], 4.31 [t, 2 H, J = 7 Hz, CH_2O], 7.40 [ddd, 2 H, J = 7.5, 5.0, 1.0 Hz, H5,5''], 7.92 [dt, 2 H, J = 8.0, 7.6, 1.8 Hz, H4,4''], 8.08 [s, 2 H, H3',5'], 8.69 [ddd, 2 H, J = 8.0, 2.0, 1.0 Hz, H3,3''], 8.79 [ddd, 2 H, J = 5.0, 2.0, 1.0 Hz, H6,6''] DCI-MS; *m/z* (%): 362 (100) [MH^+] $C_{23}H_{27}N_3O$ (361.0).

2-Hydroxyethanethiolate-(4'-n-octyloxy-2,2':6',2''-terpyridine) platinum(II) nitrate

The title complex was prepared by a method analogous to (**1,A_{het}.N**).Yield (110 mg, 83%) (Found: C, 43.5; H, 4.8; N, 8.2. Calc. for $C_{25}H_{32}SN_4O_5Pt$: C, 43.2; H, 4.6; N, 8.1%). ^{1}H NMR (DMSO): δ = 0.96 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.94 [m, 2 H, (CH_2CH_2O)], 2.55 [t, 2 H, J = 7 Hz, SCH_2], 3.58 [t, 2 H, J = 7 Hz, $HOCH_2$], 4.34 [t, 2 H, J = 7 Hz, CH_2O], 4.79 [s, 1 H, O*H*], 7.89 [t, 2 H, J = 7.0 Hz, H5,5''], 8.22 [s, 2 H, H3',5'], 8.38 [t, 2 H, J = 7.0 Hz, H4,4''], 8.52 [d, 2 H, J = 8.0 Hz, H3,3''], 9.22 [d, 2 H, J = 6.0 Hz, H6,6'']

2-Hydroxyethanethiolate-(4'-p-bromophenyl-2,2':6',2''-terpyridine) platinum(II) nitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2''-terpyridine) platinum (II) nitrate (**1, A_{het}.N**).

Yield (111 mg, 77%). (Found: C, 37.0; H, 2.9; N, 7.7. Calc. for $C_{23}H_{19}SBrN_4O_4Pt$. $2H_2O$: C, 37.1; H, 3.1; N, 7.5%). ^1H NMR (DMSO): δ = 2.55 [t, 2 H, J = 7 Hz, SCH_2], 3.58 [t, 2 H, J = 7 Hz, $HOCH_2$], 7.89 [m, 4 H, H5,5'' + H3''',5'''], 8.07 [d, 2 H, J = 8 Hz, H2''',6'''], 8.43 [t, 2 H, J = 7.0 Hz, H4,4''], 8.61 [d, 2 H, J = 8.0 Hz, H3,3''], 8.90 [s, 2 H, H3',5'], 9.20 [d, 2 H, J = 6.0 Hz, H6,6''].

2-Hydroxyethanethiolate-(4'-p-tolyl-2,2':6',2''-terpyridine) platinum(II) nitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate (**1, A_{het}.N**). Yield (110 mg, 83%) (Found: C, 41.9; H, 3.5; N, 8.1. Calc. for $C_{24}H_{22}SN_4O_4Pt$. $2H_2O$: C, 42.4; H, 3.8; N, 8.2%). ^1H NMR (DMSO): δ = 0.96 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.94 [m, 2 H, (CH_2CH_2O)], 2.55 [t, 2 H, J = 7 Hz, SCH_2], 3.58 [t, 2 H, J = 7 Hz, $HOCH_2$], 4.34 [t, 2 H, J = 7 Hz, CH_2O], 4.79 [s, 1 H, *OH*], 7.89 [t, 2 H, J = 7.0 Hz, H5,5''], 8.22 [s, 2 H, H3',5'], 8.38 [t, 2 H, J = 7.0 Hz, H4,4''], 8.52 [d, 2 H, J = 8.0 Hz, H3,3''], 9.22 [d, 2 H, J = 6.0 Hz, H6,6''].

Pyridine-2-thiolate-(4'-n-butyloxy-2,2':6',2''-terpyridine) platinum(II) bisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate (**1, A_{het}.N**). Yield (88 mg, 69 %). (Found: C, 38.4; H, 4.0; N, 11.1. Calc. for $C_{24}H_{24}SN_6O_7Pt$. H_2O: C, 38.3; H, 3.6; N, 11.2%). ^1H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.55 [m, 2 H, (CH_2CH_3)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.45 [t, 2 H, J = 7 Hz, CH_2O], 6.92 [t, 1 H, J = 7 Hz, NCHCHC*H*], 7.36 [t, 1 H, J = 7.0 Hz, NCHC*H*]], 7.59 [d, 1 H, J = 8 Hz, SCC*H*], 7.81 [t, 2 H, J = 7.0 Hz, H5,5''], 8.12 [d, 1 H, J = 8 Hz, SCNC*H*], 8.31 [s, 2 H, H3',5'], 8.42 [t, 2 H, J = 7.0 Hz, H4,4''], 8.68 [d, 2 H, J = 8.0 Hz, H3,3''], 9.10 [d, 2 H, J = 6.0 Hz, H6,6''].

Pyridine-2-thiolate-(4'-n-hexyloxy-2,2':6',2''-terpyridine) platinum(II) bisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate (**1, A_{het}.N**). Yield (100 mg, 75%) (Found: C, 40.4; H, 3.9; N, 11.0. Calc. for $C_{26}H_{28}SN_6O_7Pt$: C, 40.9; H, 3.7; N, 11.0%). ^1H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 6 H, ($CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.45 [t, 2 H, J = 7 Hz, CH_2O], 6.92 [t, 1 H, J = 7 Hz, NCHCHC*H*], 7.36 [t, 1 H, J = 7.0 Hz, NCHC*H*]], 7.59 [d, 1 H,

J = 8 Hz, SCC*H*], 7.81 [t, 2 H, J = 7.0 Hz, H5,5''], 8.12 [d, 1 H, J = 8 Hz, SCNC*H*], 8.31 [s, 2 H, H3',5'], 8.42 [t, 2 H, J = 7.0 Hz, H4,4''], 8.68 [d, 2 H, J = 8.0 Hz, H3,3''], 9.10 [d, 2 H, J = 6.0 Hz, H6,6''].

Pyridine-2-thiolate-(4'-n-octyloxy-2,2':6',2''-terpyridine) platinum(II) bisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate (**1**, A_{het}-**N**). Yield (110 mg, 80%). (Found: C, 41.8; H, 4.3; N, 10.5. Calc. for $C_{28}H_{32}SN_6O_7Pt$. H_2O: C, 41.5; H, 4.2; N, 10.4%). ^{1}H NMR (DMSO): δ = 0.98 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.41 [t, 2 H, J = 7 Hz, CH_2O], 6.92 [t, 1 H, J = 7 Hz, NCHCHC*H*], 7.36 [t, 1 H, J = 7.0 Hz, NCHC*H*]], 7.59 [d, 1 H, J = 8 Hz, SCC*H*], 7.81 [t, 2 H, J = 7.0 Hz, H5,5''], 8.12 [d, 1 H, J = 8 Hz, SCNC*H*], 8.31 [s, 2 H, H3',5'], 8.42 [t, 2 H, J = 7.0 Hz, H4,4''], 8.68 [d, 2 H, J = 8.0 Hz, H3,3''], 9.10 [d, 2 H, J = 6.0 Hz, H6,6''] 7.36 [t, 1 H, J = 7.0 Hz, NCHC*H*], 7.50 [d, 2 H, J = 8 Hz, H3''',5'''], 7.59 [d, 1 H, J = 8 Hz, SCC*H*], 7.85 [t, 2 H, J = 7.0 Hz, H5,5''], 8.14 [m, 3 H, SCNC*H* + H2''',6'''], 8.43 [t, 2 H, J = 7.0 Hz, H4,4''], 8.80 [d, 2 H, J = 8.0 Hz, H3,3''], 9,00 [s, 2 H, H3',5'], 9.11 [d, 2 H, J = 6.0 Hz, H6,6''].

Pyridine-4-thiolate-(4'-n-butyloxy-2,2':6',2''-terpyridine) platinum(II) bisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate. Yield (100 mg, 78 %). (Found: C, 38.3; H, 4.1; N, 11.4. Calc. for $C_{24}H_{24}SN_6O_7Pt$: C, 38.3; H, 3.6; N, 11.2%). ^{1}H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.55 [m, 2 H, (CH_2CH_3)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.42 [t, 2 H, J = 7 Hz, CH_2O], 7.81 [t, 2 H, J = 7.0 Hz, H5,5''], 8.12 [d, 2 H, J = 7 Hz, SCN(CHC*H*)$_2$], 8.22 [d, 2 H, J = 7 Hz, SCN(C*H*)$_2$],8.36 [s, 2 H, H3',5'], 8.48 [t, 2 H, J = 7.0 Hz, H4,4''], 8.68 [d, 2 H, J = 8.0 Hz, H3,3''], 8.82 [d, 2 H, J = 6.0 Hz, H6,6''] .

Pyridine-4-thiolate-(4'-n-hexyloxy-2,2':6',2''-terpyridine) platinum(II) bisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2"-terpyridine) platinum (II) nitrate. Yield (108 mg, 81%). (Found: C, 41.2; H, 4.0; N, 11.5. Calc. for $C_{26}H_{28}SN_6O_7Pt$: C, 40.9; H, 3.7; N, 11.0%). ^{1}H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 6 H,

($CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.45 [t, 2 H, J = 7 Hz, CH_2O], 7.84 [t, 2 H, J = 7.0 Hz, H5,5''], 8.17 [d, 2 H, J = 7 Hz, SCN(CHC*H*)$_2$], 8.28 [d, 2 H, J = 7 Hz, SCN(CH)$_2$],8.42 [s, 2 H, H3',5'], 8.54 [t, 2 H, J = 7.0 Hz, H4,4''], 8.74 [d, 2 H, J = 8.0 Hz, H3,3''], 8.91 [d, 2 H, J = 6.0 Hz, H6,6''] .

Pyridine-4-thiolate-(4'-n-octyloxy-2,2':6',2''-terpyridine) platinum(II) bisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2''-terpyridine) platinum (II) nitrate. Yield (110 mg, 78%). (Found: C, 42.0; H, 4.4; N, 11.1. Calc. for $C_{28}H_{32}SN_6O_7Pt$: C, 42.5; H, 4.1; N, 10.6%). ^{1}H NMR (DMSO): δ = 0.98 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.41 [t, 2 H, J = 7 Hz, CH_2O], 7.84 [t, 2 H, J = 7.0 Hz, H5,5''], 8.17 [d, 2 H, J = 7 Hz, SCN(CHC*H*)$_2$], 8.28 [d, 2 H, J = 7 Hz, SCN(CH)$_2$],8.40 [s, 2 H, H3',5'], 8.52 [t, 2 H, J = 7.0 Hz, H4,4''], 8.61 [d, 2 H, J = 8.0 Hz, H3,3''], 8.89 [d, 2 H, J = 6.0 Hz, H6,6''].

Imidazole-2-thiolate-bis[(4'-n-butyloxy-2,2':6',2''-terpyridine) platinum(II)] trinitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2'' -terpyridine) platinum (II) nitrate. Yield (100 mg, 78 %). (Found: C, 35.9; H, 3.0; N, 12.0. Calc. for $C_{41}H_{41}SN_{11}O_{11}Pt_2$: C, 36.1; H, 3.0; N, 11.4%). ^{1}H NMR (DMSO): δ = 1.02 [t, 3 H, J = 7 Hz, CH_3], 1.55 [m, 2 H, (CH_2CH_3)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.42 [t, 2 H, J = 7 Hz, CH_2O], 7.81 [t, 2 H, J = 7.0 Hz, H5,5''], 8.12 [d, 2 H, J = 7 Hz, SCN(CHC*H*)$_2$], 8.22 [d, 2 H, J = 7 Hz, SCN(CH)$_2$],8.36 [s, 2 H, H3',5'], 8.48 [t, 2 H, J = 7.0 Hz, H4,4''], 8.68 [d, 2 H, J = 8.0 Hz, H3,3''], 8.82 [d, 2 H, J = 6.0 Hz, H6,6''] .

Imidazole-2-thiolate-bis[(4'-n-hexyloxy-2,2':6',2''-terpyridine) platinum(II)]

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2'' -terpyridine) platinum (II) nitrate. Yield (60 mg, 47%). (Found: C, 38.3; H, 3.4; N, 10.9. Calc. for $C_{45}H_{49}SN_{11}O_{11}Pt_2$: C, 38.1; H, 3.5; N, 10.9%). ^{1}H NMR (D_2O): δ = 0.91 [t, 6 H, J = 7 Hz, CH_3], 1.35 [m, 8 H, (2 x $CH_2CH_2CH_2CH_3$)], 1.50 [m, 4 H, 2 x $CH_2CH_2CH_2CH_3$] 1.94 [m, 4 H, (CH_2CH_2O)], 4.30 [t, 4 H, J = 7 Hz, CH_2O], 7.21 [d, 1 H, J = 6 Hz, HNC*H*CHNPt] 7.38 [t, 4 H, J = 7.0 Hz, H5,5''], 7.38 [d, 1 H, J = 6 Hz, HNCHC*H*NPt], 7.52 [s, 4 H, H3',5'], 7.76 [d,

2 H, J = 6.0 Hz, H6,6'' bound through N], 7.89 [d, 4 H, J = 8.0 Hz, H3,3''], 8.13 [t, 4 H, J = 7.0 Hz, H4,4''], 8.61 [d, 2 H, J = 6.0 Hz, H6,6'' bound through S].

Imidazole-2-thiolate-bis[(4'-n-octyloxy-2,2':6',2''-terpyridine) platinum(II)]trisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2''-terpyridine) platinum (II) nitrate. Yield (110 mg, 78%). (Found: C, 39.9; H, 4.2; N, 10.3. Calc. for $C_{49}H_{57}SN_{11}O_{11}Pt_2$: C, 39.9; H, 3.9; N, 10.5%). ^{1}H NMR (DMSO): δ = 0.98 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.41 [t, 2 H, J = 7 Hz, CH_2O], 7.84 [t, 2 H, J = 7.0 Hz, H5,5''], 8.17 [d, 2 H, J = 7 Hz, SCN(CHCH)$_2$], 8.28 [d, 2 H, J = 7 Hz, SCN(CH)$_2$],8.40 [s, 2 H, H3',5'], 8.52 [t, 2 H, J = 7.0 Hz, H4,4''], 8.61 [d, 2 H, J = 8.0 Hz, H3,3''], 8.89 [d, 2 H, J = 6.0 Hz, H6,6''] .

Imidazole-2-thiolate-bis[(4'-p-bromophenyl-2,2':6',2''-terpyridine) platinum(II)] trisnitrate

The title complex by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2''-terpyridine) platinum (II) nitrate. Yield (110 mg, 78%). (Found: C, 36.7; H, 2.5; N, 11.0. Calc. for $C_{45}H_{31}SBr_2N_{11}O_9Pt_2 . H_2O$: C, 36.8; H, 2.3; N, 10.5%). ^{1}H NMR (DMSO): δ = 0.98 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.41 [t, 2 H, J = 7 Hz, CH_2O], 7.84 [t, 2 H, J = 7.0 Hz, H5,5''], 8.17 [d, 2 H, J = 7 Hz, SCN(CHCH)$_2$], 8.28 [d, 2 H, J = 7 Hz, SCN(CH)$_2$],8.40 [s, 2 H, H3',5'], 8.52 [t, 2 H, J = 7.0 Hz, H4,4''], 8.61 [d, 2 H, J = 8.0 Hz, H3,3''], 8.89 [d, 2 H, J = 6.0 Hz, H6,6''] .

Imidazole-2-thiolate-bis[(4'-p-tolyl-2,2':6',2''-terpyridine) platinum(II)] trisnitrate

The title complex was prepared by a method analogous to the preparation of 2-hydroxyethanethiolate-(2,2':6',2''-terpyridine) platinum (II) nitrate. Yield (110 mg, 78%). (Found: C, 38.7; H, 3.4; N, 10.9. Calc. for $C_{47}H_{37}SN_{11}O_9Pt_2 . 6H_2O$: C, 39.4; H, 3.4; N, 10.8%). ^{1}H NMR (DMSO): d = 0.98 [t, 3 H, J = 7 Hz, CH_3], 1.45 [m, 10 H, ($CH_2CH_2CH_2CH_2CH_2CH_3$)], 1.97 [m, 2 H, (CH_2CH_2O)], 4.41 [t, 2 H, J = 7 Hz, CH_2O], 7.84 [t, 2 H, J = 7.0 Hz, H5,5''], 8.17 [d, 2 H, J = 7 Hz, SCN(CHCH)$_2$], 8.28 [d, 2 H, J = 7 Hz, SCN(CH)$_2$],8.40 [s, 2 H, H3',5'], 8.52 [t, 2 H, J = 7.0 Hz, H4,4"],

8.61 [d, 2 H, J = 8.0 Hz, H3,3"], 8.89 [d, 2 H, J = 6.0 Hz, H6,6"].

Pyridine-2-thiolate-(4'-p-bromophenyl-2,2':6',2''-terpyridine)platinum(II) bisnitrate

The title complex was prepared as above with only an equal amount of fourth ligand, yield (110 mg, 80%). (Found: C, 37.4; H, 2.7; N, 10.1. Calc. for $C_{26}H_{19}SBrN_6O_6Pt$. H_2O: C, 37.3; H, 2.5; N, 10.0%). ^1H NMR (DMSO): δ = 6.92 [t, 1 H, J = 7 Hz, NCHCHC*H*], 7.36 [t, 1 H, J = 7.0 Hz, NCHC*H*], 7.59 [d, 1 H, J = 8 Hz, SCC*H*], 7.85 [t, 2 H, J = 7.0 Hz, H5,5''], 7.92 [d, 2 H, J = 8 Hz, H3''',5'''], 8.14 [m, 3 H, SCNC*H* + H2''',6'''], 8.43 [t, 2 H, J = 7.0 Hz, H4,4"], 8.80 [d, 2 H, J = 8.0 Hz, H3,3"], 9,10 [s, 2 H, H3',5'], 9.11 [d, 2 H, J = 6.0 Hz, H6,6"].

Pyridine-2-thiolate-(4'-p-tolyl-2,2':6',2''-terpyridine)platinum(II) bisnitrate

The title complex was prepared as above with only an equal amount of fourth ligand, yield (110 mg, 80%). (Found: C, 39.8; H, 3.6; N, 10.1. Calc. for $C_{27}H_{22}SN_6O_6Pt$: C, 39.3; H, 3.6; N, 10.2%). ^1H NMR (DMSO): d = 2.51 [s, 3 H, CH_3], 6.92 [t, 1 H, J = 7 Hz, NCHCHC*H*], 7.36 [t, 1 H, J = 7.0 Hz, NCHC*H*], 7.50 [d, 2 H, J = 8 Hz, H3''',5'''], 7.59 [d, 1 H, J = 8 Hz, SCC*H*], 7.85 [t, 2 H, J = 7.0 Hz, H5,5"], 8.14 [m, 3 H, SCNC*H* + H2''',6'''], 8.43 [t, 2 H, J = 7.0 Hz, H4,4"], 8.80 [d, 2 H, J = 8.0 Hz, H3,3"], 9,00 [s, 2 H, H3',5'], 9.11 [d, 2 H, J = 6.0 Hz, H6,6"].

Results

Antiprotozoal Activity

2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) shows a wide range of antiprotozoal activity (Tables 1 to 3). Against *Leishmania donovani* it has ED_{50} = 3μM which is comparable with complexes with the best leaving groups, namely water or ammonia in the aqua- and ammine-2,2':6',2"-terpyridine-platinum(II) complexes respectively (WO 97/27202). This suggests that either intercalation into DNA is the mechanism of antiprotozoal action of this complex or that there is an enzyme which is inhibited by it. 2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) is even more effective against *Trypanosoma cruzi* and *Trypanosoma brucei* (Tables 2 and 3).

Trypanothione reductase is an FAD-dependent enzyme which catalyses the reduction of trypanothione using NADPH as co-factor. The enzyme is found in the

haemflagellate protozoa from the genera *Trypanosoma* and *Leishmania* and is a known target for drugs against these parasites. 2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) reversibly inhibits trypanothione reductase from *Trypanosoma cruzi* in the absence of NADPH with K_i=60μM at pH 7.5. The enzyme (3nM), however, is 95% inactivated in 20 min. by 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) (40μM) in the presence of NADPH (20μM). From a full kinetic analysis the second order rate constant for irreversible inhibition, k_i = 2400 $M^{-1}s^{-1}$. From these observations is would seem that irreversible inactivation occurs by platination of the active site thiol group of Cys-52 generated from the Cys-52-Cys-63 disulphide bridge in the presence of NADPH.

Another possible target for 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) inhibition is tryparedoxin a thioredoxin-like protein found in trypanosomes which with trypanothione is an effective reductant of trypanosomal ribonucleotide reductase an enzyme required for the biosynthesis of deoxyribonucleotides in trypanosomes.

In the light of the above considerations further 2,2':6',2"-terpyridine-platinum(II) complexes have been investigated and the data for complexes (**2**) to (**11**) are shown in Tables 1 to 3.

The data in Table 1 show that all the 2,2':6',2"-terpyridine platinum(II) thiolate complexes possess higher activity against *Leishmania donovani* than pentostam. Y_{het}.N (**3**) and I_{25}.N (**8**) possess the highest activity having ED_{50} values below 1 µg/ml.

The data in Table 2 show that three of the 2,2':6',2"-terpyridine platinum(II) thiolate complexes have ED_{50} values at or below 1 µg/ml and one of them Y_{het}.N (**3**) is below 0.1 µg/ml against *Trypanosoma cruzi*. These data compare very favourably with benzimidazole at 7.45 µg/ml.

The data in Table 3 show that all of the 2,2':6',2"-terpyridine platinum(II) thiolate complexes have ED_{50} values below 1 µg/ml and three of them have values between 0.02-0.03 µg/ml against *Trypanosoma brucei*. These data compare very favourably with pentamidine.

The antiprotozoal activity of the 2,2':6',2"-terpyridine platinum(II) thiolate

complexes appears to be remarkably insensitive to the nature of the thiolate ligand. It might have been expected that the pKa of the thiolate would be an important parameter but, for example $I_{het}.N$ (**2**) with 2-hydroxyethanethiolate as the fourth ligand is somewhat more active the $I_{27}.N$ (**10**) with diethylphosphorothioate as the fourth ligand against *T.cruzi* (Table 2) and *T.brucei* (Table 3).

2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) was tested *in vivo* in BALB/c mice challenged with *Leishmania donovani*. Six days post infection (**1**) was administered intra-peritoneally at 50mg/kg per day for five days which lead to 39% inhibition compared with the control group of mice. All the mice survived this regime (Table 4).

The *in vivo* activity of $Y_{het}.N$ (**3**) and $I_{25}.N$ (**8**) against *Leishmania donovani* and *Trypanosoma brucei rhodensiense* (ST/B900) is shown in Table 4. The compounds were administered at 50 mg/kg, which is below the maximum tolerated dose. All the mice which had been challenged with a lethal dose of *Trypanosoma brucei rhodensiense* survived when given $Y_{het}.N$ (**3**) at 50 mg/kg whereas all the control group died after 14.6 ± 1.5 days.

It is clear from these results that thiolate-2,2':6',2"-terpyridine-platinum(II) complexes have considerable potential as antiprotozoal agents.

Antirheumatoid Arthritic Activity

Human thioredoxin reductase is now considered to be the site of action of organogold compounds such as aurothioglucose (S. Gromer *et al.*, *J. Biol. Chem.*, **1998**, *273*, 20096-20101) and auranofin which are used in the treatment of rheumatoid arthritis. Thus the thiolato-2,2':6',2"-terpyridine-platinum(II) complexes are likely to be agents useful in the treatment of rheumatoid arthritis. The 2,2':6',2"-terpyridine-platinum(II) analogue of aurothioglucose, i.e. (**12**) has been prepared and at 20μM concentration irreversibly inhibits human thioredoxin reductase within 10 min. in the presence of NADPH.

Human thioredoxin reductase is also a homodimeric FAD-dependent enzyme and has been recently shown to be a seleno-enzyme. Only two other mammalian enzymes are known to contain selenocysteine, namely, glutathione peroxidases and thyroxine deiodinases. The selenocysteine forms a seleno-sulphide bridge at the

active site analogous to the many disulphide oxidoreductases. In its reduced form the enzyme is inhibited by organic gold compounds (e.g. auranofin) used in the treatment of rheumatoid arthritis. Since selenocysteine is sufficiently nucleophilic to displace thiols from 2,2':6',2"-terpyridine-platinum(II) complexes, this is likely to be the site of platination by 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) and other thiolate-2,2':6',2'-terpyridine Pt(II) complexes, e.g. (**2**) and (**3**) leading to the inactivation human thioredoxin reductase. Thus 2,2':6',2"-terpyridine-platinum(II) thiolate complexes are possible candidates for the treatment of rheumatoid arthritis.

Antitumour Activity

2-Hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) is shown to possess antitumour activity against a number of human ovarian tumour cell lines (Table 5). However, displacement of the hydroxyethanethiol ligand by a nuclear base to form a covalent link with DNA has been shown not to occur (M. Howe-Grant *et al.*, *Biochemistry*, **1976**, *15*, 4339-4346). Intercalation into DNA is a possible mechanism of action but platination of an enzyme is also probable. Although 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) is more effective than carboplatin against some tumour cell lines, e.g. CH1cis^R, A2780, A2780cis^R and SKOV-3, it is less effective than cisplatin and 2,2':6',2"-terpyridine-platinum(II) complexes with better leaving groups as the fourth ligand, which are known to be capable of platinating guanine residues in DNA. Nevertheless carboplatin is currently the agent of choice for the treatment of women with ovarian cancer.

It was considered that the antitumour activity of 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**) could be due in part to its inhibition of human thioredoxin reductase. Thioredoxin is a small protein which in its reduced state is the specific reductant in the conversion of ribonucleotides to 2'-deoxyribonucleotides by ribonucleotide reductase. As such it is essential for the generation in eukaryotes of the 2'-deoxyribonucleotides required for DNA synthesis. This hypothesis has been tested. Initially it was shown that human thioredoxin reductase in the presence of NADPH was virtually completely inactivated in 10 min. by 20 μM 2-hydroxyethanethiolato-2,2':6',2"-terpyridine-platinum(II) (**1**). Since human thioredoxin reductase contains the rare selenocysteine residue in its active site, it is

likely that this is the site of platination. In the oxidised enzyme this residue is cross-linked with a cysteine, accounting for the failure of (**1**) to irreversibly inhibit the enzyme in the absence of NADPH. A number of thiolate 2,2':6',2"-terpyridine platinum (II) complexes have been investigated.

The inhibition of hTrxR by the platinum complexes shows a mixed type inactivation pattern. Two major setups were chosen to characterise this inhibition for the nine platinum complexes in more detail (data are summarised in Table 6): For determining the inhibition constants (Ki) for the competitive components of the inhibition appr. 2 nM hTrxR was mixed with various concentrations of DTNB (50 µM-1 mM) and one inhibitor concentration (10 nM-1 µM depending on the inhibitor) in assay buffer (total volume 1 ml). The reactions were started with 200 µM NADPH at 25°C. In parallel the Km-value for DTNB in the absence of inhibitor was determined. Ki-values for competitive inhibition was calculated according to the following equation:

$$Ki=Km\ [I]/(Km'-Km)$$

To characterise the tight binding component of the inhibition, 2 nM hTrxR is assay buffer was reduced with 200 µM NADPH; then, different concentrations of the respective inhibitor were added, the assay was incubated for 5 min at 25°C and started with 3 mM DTNB. IC_{50}-values were calculated from the dose-response curves. Since the enzyme has to be reduced for the tight binding inhibition and on the other hand at 3 mM DTNB the competitive component of the inhibition is very weak, the two different experimental setups sufficiently describe the respective component of inhibition.

The thiolate 2,2':6',2"-terpyridine platinum (II) complexes (**2**), (**3**) and (**12**), each at a concentration 20μM irreversibly inhibited human thioredoxin reductase within 10 min. in the presence of NADPH.

It was considered that the biological activity may correlate with the leaving ability of the thiolate ligand which should be linked to the pKa of the thiol. When 2-mercaptopyridine and 4-mercaptopyridine were incorporated as the fourth ligand in 2,2':6',2"-terpyridine-platinum(II) complexes, sulphur (as expected) was the preferred ligand giving the thiolate 2,2':6',2"-terpyridine-platinum(II) complexes e.g.

I_{25}.N (**8**) and I_{23}.N (**6**). Similarly 2-mercapto-pyrimidine gave thiolate 2,2':6',2"-terpyridine-platinum(II) complex e.g. I_{24}.N (**7**). When 2-mercapto-imidazole or 2-mercaptobenzimidazole were used, however, bis-platinum complexes were formed e.g. I_{21}.2N (**4**) and I_{22}.2N (**5**) respectively. This can be rationalised by postulating that the initial site of platination is at sulphur but that the close proximity of the positive charge on platinum to the NH group so lowers it pKa that it loses a proton and the negatively charge nitrogen is then rapidly platinated to give the bis-platinated product. The bis-platinated complexes are interesting as antitumour agents as they may have the ability to intercalate into DNA through the thiolate 2,2':6',2"-terpyridine-platinum(II) complex and platinate DNA through the second platinum complex. The possibility of using thiols with a wide range of pK_as, differing charge and lipophilicity as the fourth ligand in 2,2':6',2"-terpyridine-platinum(II) complexes may make it possible to modulate the biological activity of these systems. Thus dithiophosphate O,O-diesters have low pKa values and their hydrophobicity may be controlled by the nature of the ester groups. The 2,2':6',2"-terpyridine-platinum(II) complexes retain a single positive charge. If thiosulphate is used as the fourth ligand, the complex becomes overall neutral.

The 2,2':6',2"-terpyridine platinum(II) complexes (**4**) to (**9**) have also been shown to possess anti-tumor activity against a number of human ovarian tumor cell lines. The results are presented in Table 5. Complex (**4**) is more effective than cisplatin against all the human ovarian tumor cell lines except A2780. A number of the other complexes are more effective than cisplatin against the cisplatin resistant cell lines and some are very effective against the highly refractory cell line SKOV3.

Thioredoxin is involved in a range of essential cellular regulatory processes the most prominent being the donation of electrons to ribonucleotide reductase and the selenoenzyme human thioredoxin reductase (hTrxR; EC 1.6.4.5) is a possible target for antitumour chemotherapy. Malignant neoplasms of the brain represent the second leading cause of cancer related mortality in children under the age of 15. The prognosis of patients with glioblastoma multiforme, the most malignant type of gliomas, remains poor offering a median survival time of only 1 year.

The NADPH-reduced hTrxR is inhibited almost stoichiometrically by the

2,2':6',2"-terpyridine platinum(II) complexes involving a competitive and a tight binding component. From a study of the inhibition of hTrxR by a number these complexes (Table 6) imidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum(II)] bisnitrate, I_{21}.2N (**4**), and N,S-bis[(2,2':6',2"-terpyridine)platinum(II)] thioacetimine trisnitrate, A_{26}.3N (**9**), were selected for further study. For the most potent inhibitor, N,S-bis[(2,2':6',2"-terpyridine)platinum(II)] thioacetimine trisnitrate, the Ki for the competitive component of the inhibition is 4 nM, the IC_{50} for the tight binding component is 2 nM after an incubation time of 5 min. The closely related but non selenium-containing enzyme human glutathione reductase is much less inhibited (by a factor of >2000). A single dose (10 μM) of the above inhibitors reduced proliferation of several highly malignant glioblastoma cell lines by more than 95 % within 3 days (Table 7 and 8).

The 2,2':6',2"-terpyridine platinum(II) complexes (**4**), (**6**), (**9**) and (**17**) have also been tested in vitro against other tumor cell lines with 96 hours continuous exposure (Table 9). The complexes are most effective against colon tumour cell lines.

Table 1. ***In vitro*** **Antiprotozoal Activity of Pt(II) thiolate complexes against** ***Leishmania donovani***

Compound	% Inhibition at concentrations in µg/ml					ED_{50} (µg/ml)	TX ED_{50} (µg/ml)
	30	10	3	1	0.3		
A_{het}.N **(1)**	99.8	99.3	63.3	0		3.05	8.4
I_{het}.N **(2)**	t/100	98.5	86.6	2.3		2.31	
Y_{het}.N **(3)**	t/100	t/100	t/100	98.5		<1	
I_{21}.2N **(4)**	98.2	97.2	10.6	1.01		5.03	
I_{22}.2N **(5)**	97	97.9	30.1	1.77		4.08	
I_{23}.N **(6)**	97	96.4	16.7	0		4.78	
I_{24}.N **(7)**	99.5	98.5	66.8	2.78		2.77	
I_{25}.N **(8)**	t/100	99.5	98.9	88.5	8.24	0.67	4.3
A_{26}.3N **(9)**	t/100	97.2	94.5	41.2	2.2	1.26	6.2
I_{27}.N **(10)**	99.7	99.1	92.4	34.9		1.38	
A_{MS}.N **(11)**	100	95.7	86.3	0		2.9	

Key: t/100 = toxic to macrophages, no parasites present

TX = cytotoxicity

Pentostam ED_{50} = 8.45 µgSb^{v}/ml

Table 2. ***In vitro*** **Antiprotozoal Activity of Pt(II) thiolate complexes against** ***Trypanosoma cruzi***

Compound	% Inhibition at concentrations in μg/ml						ED_{50} (μg/ml)
	30	10	3	1	0.3	0.1	
A_{het}.N **(1)**	t/100	t/100	t/100	90.8	66.1	38.9	0.15
I_{het}.N **(2)**	t/+	t/+	t/+	64.9	60.3	32.6	0.25
Y_{het}.N **(3)**	t/100	t/100	t/100	88.7	77.4	58.6	<0.1
I_{25}.N **(8)**	34.7	0					>30
A_{26}.3N **(9)**	27	2.7	0				>30
I_{27}.N **(10)**	99.7	99.1	92.4	34.9			1.38
A_{MS}N **(11)**	t/100	t/+	3.75	0			

Key: t/100 = toxic to macrophages, no parasites present

t/+ = toxic to macrophages, parasites present

Control: Benzimidazole ED_{50} = 7.45 μg/ml

Table 3. ***In vitro* Antiprotozoal Activity of Pt(II) thiolate complexes against *Trypanosoma brucei* and *Trypanosoma brucei rhodesiense STIB900***

Compound	Parasite	% Inhibition at concentrations in µg/ml								ED_{50} (µg/ml)
		30	10	3	1	0.3	0.1	0	0	
A_{het}.N **(1)**	*T. brucei*	100	100	100	100	100	100	66	36	0.02
I_{het}.N **(2)**	*T. brucei*	100	100	100	100	100	100	84	17	0.02
Y_{het}.N **(3)**	*T. brucei*	100	100	100	100	100	100	20	0	0.03
I_{25}.N **(8)**	*T.b.rhod.*	95	96	93.6	87	3.5	0.4	0		0.7
A_{26}.3N **(9)**	*T.b.rhod.*	95	99	100	93	23	17	11	8.1	0.5
I_{27}.N **(10)**	*T.b.rhod.*	99	99	98.9	96	64	0			0.3
A_{MS}N **(11)**	*T.b.rhod.*	97	98	97.9	70	0				0.9

Control: Pentamidine 100% inhibition at 1 µg/ml

Table 4. ***In vivo* activity of Terpyridine platinum(II) complexes against *Leishmania donovani* and *Trypanosoma brucei rhodesiense* *(ST/B900)***

In vivo anti-leishmanial activity

Compound	Dose	Inhibition
$A_{het.}N$ (**1**)	50 mg/kg i.p. x 5	39%
$I_{25}.N$ (**8**)	50 mg/kg i.p. x 5	52.7%
$Y_{het.}N$ (**3**)	50 mg/kg i.p. x 5	26.0%

In vivo anti-trypanosomal activity

Compound	Dose	Mean days survival
$I_{25}.N$ (**8**)	50 mg/kg i.p. x 4	15.0±0.7
$Y_{het.}N$ (**3**)	50 mg/kg i.p. x 4	All survived
Untreated control	-	14.6±1.5

Table 5. **The 96 hour IC_{50} values of Pt(II) thiolate complexes in (μM) for the *in vitro* growth inhibition of human ovarian cell lines compared with cisplatin and carboplatin**

Two of the cell lines are resistant to cisplatin

RF is the resistance factor: IC_{50} resistant line/IC_{50} parent line

Compound	CH1	CH1cis^R	RF	CH1dox^R	RF	A2780	A2780cis^R	RF	SKOV-3
cisplatin	0.4	1.2	3			0.53	8.8	16.6	2.25
carboplatin	6.2	14	2.3			35	>100	-	>100
A_{het}.N (1)	14	12.5	0.9	11.5	0.8	18	20	1.1	18
I_{21}.2N (4)	0.195	0.4	2			1.95	1.75	0.9	0.68
I_{22}.2N (5)	0.45	0.46	1			2.2	1.7	0.8	0.68
I_{23}.2N (6)	0.51	1.35	2.6			2.45	2.95	1.2	2.6
I_{24}.2N (7)	0.49	0.86	1.7			2.25	2.8	1.2	3.15
I_{25}.N (8)	2.1	2.2	1			18.5	10	0 5	2.9
A_{21}.2N (13)	0.5	0.68	1.4			6	3.6	0.6	1.8
A_{22}.2N (14)	0.58	0.76	1.3			2.3	2.6	1.1	1.7
A_{23}.2N (15)	1.85	2.85	1.5			11.5	9.6	0.8	4.75
A_{24}.2N (16)	1.3	1.8	1.4			2.9	4.15	1.4	4.0
A_{26}.3N (9)	2.5	2.3	0.9			10	9	0.9	4.2

Table 6. **Inhibition of isolated human thioredoxin reductase (hTrxR) and recombinant glutathione reductase (hGR) by platinum complexes. Given are: absence of inhibitor, the Km'-value for DTNB in the presence of the inhibitor, the inhibitor concentration under which the Km'-value was determined, inhibition, the IC_{50}-value of the platinum complexes inhibiting hTrxR obtained with varying inhibitor concentrations under standard assay conditions and the inhibition of hGR by 10 μM of the platinum complexes after 2 min incubation in the enzyme assay.**

Compound	Km hTrxR [μM]	Km' [μM]	[I] for Km' [μM]	Ki, comp. [nM]	IC_{50} [nM]	hGR% inh. at 10 μM
A_{het}.N (1)	103	399	1	348	35	7
Y_{het}.N (3)	103	177	0.1	139	200	49
A_{tgl}.N (12)	103	408	1	337	25	35
I_{het}.N (2)	103	4738	1	22	30	55
I_{21}.2N (4)	103	1007	0.1	11	3	20
I_{23}.N (6)	103	1055	0.05	5	4	90
I_{24}.N (7)	103	715	0.1	17	7	66
I_{25}.N (8)	103	247	0.01	7	6	47
A_{26}.3N (9)	103	2723	0.1	4	2	30

Table 7. Antiproliferative effects of the platinum complex $I_{23}N$ (6) on different tumor cell lines. Shown are % proliferation of control cultures (100%)

Doses	1 μM	5 μM	10 μM	20 μM
NCH37				
1x	92+0%	76.5+4.3%	53+10.5%	8.1+2.2%
3x	95.2+0.85%	65.3+7.6%	19.2+2.3%	1.2+0.2%
NCH82				
1x	89+7.8%	66.4+0.4%	26.5+2.3%	1.1+0.3%
3x	83.1+6.0%	24.6+3.9%	2.6+0.4%	0.3+0.1%
NCH89				
1x	89.8+1.5%	8.5+1.4%	3.1+1.4%	0.8+0.35%
3x	67+3.7%	2.6+0.6%	1.6+0.4%	0.6+0.05%
HNO97				
1x	98.4+3.9%	52+7.7%	2.7+0.3%	0.1+0.1%
3x	100.3+1.0%	18.9+3.7%	0.7+0.3%	0.1+0.05%
HNO199				
1x	96.1+0.5%	88.5+3.7%	43.6+14.9%	1.2+0.05%
3x	95.5+4.1%	57.2+6.0%	5.5+2.4%	0.9+0.2%

Table 8. **Antiproliferative effects of the platinum complex $A_{26}3N$ (9) on different tumor cell lines. Shown are % proliferation of control cultures (100%).**

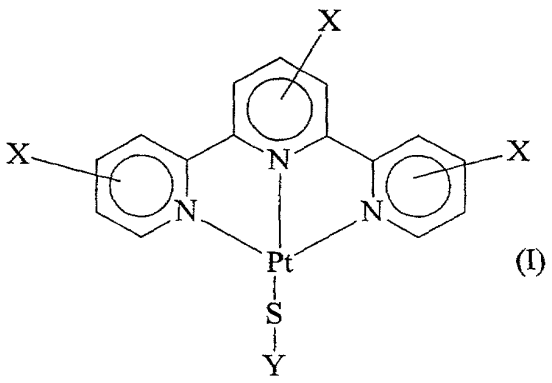
Doses	1 μM	5 μM	10 μM	20 μM
NCH37				
1x	101.3+0.5%	54+4.7%	11.7+4.7%	2+1.3%
3x	90.8+21.1%	38.5+7.6%	2.4+1.3%	1.5+1.2%
NCH82				
1x	92.8+5.7%	37+1.3%	19.8+4.2%	2.6+1.3%
3x	78.6+17.8%	23.4+0.2%	5.1+0.3%	1.7+0.05%
NCH89				
1x	79.6+14.7%	18.8+0.8%	4.2+1.5%	1.9+0.6%
3x	59.5+15.5%	6+0.3%	1.1+0.4%	0.4+0.3%
HNO97				
1x	102.9+2.4%	47.7+17.4%	7.4+3.9%	0.5+0.4%
3x	96.4+7.8%	12.2+6.5%	2.1+1.3%	0+0%
HNO199				
1x	101.3+2.3%	88.9+5.8%	15.6+10.2%	3.1+2.3%
3x	90.9+17.4%	16.7+1.1%	3.2+1.8%	0.1+0.05%

Table 9. **The 96 hour IC_{50} values of Pt(II) thiolate complexes in μM for the *in vitro* growth inhibition of MDA-N and MDA-MB-435 (Human breast), HCT116 & DLD-1 (Human colon) and MAC15A & MAC26 (Mouse colon) cell lines in RPMI medium**

Compounds	I_{21}.2N **(4)**	I_{23}.N **(6)**	A_{26}.3N **(9)**	I_{26}.3N **(17)**
MDA-N	>10	>10	>10	7.5
MDA-MB-432	>10	>10	>10	>10
HCT116	4.6	9.2	8	4.7
DLD-1	3.1	6.5	8.7	3.1
MAC15A	4.6	7.9	5.9	3.5
MAC26	>10	>10	>10	>10

CLAIMS

1. A compound which is a complex of formula (I)



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, alkylthio, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

2. A compound as claimed in claim 1 wherein X is hydrogen, halogen or alkoxyl.

3. A compound as claimed in claim 1 or 2 wherein X is hydrogen, chlorine, methoxyl, ethoxyl, propoxyl, butyloxyl, pentyloxyl, hexyloxyl, heptyloxyl, octyloxyl, bromophenyl or tolyl.

4. A compound as claimed in any one of claims 1 to 3 wherein Y is

alkyl, alkaryl, heterocyclyl or an inorganic oxyacid or inorganic oxyacid derivative.

5. A compound as claimed in any one of the preceding claims wherein Y is $(CH_2)_nOH$ or $(CH_2)_n NH_3^+$ wherein n is an integer of 1 to 6 or alkyl substituted by one or more amino or carboxy groups; CH_2aryl; a 5- or 6-membered saturated heterocyclic ring or a 5- or 6-membered unsaturated heterocyclic ring containing at least one N which may be fused to a 6-membered aryl ring; or SO_3R or PO_3R_2 wherein R is hydrogen or alkyl.

6. A compound as claimed in claim 5 wherein n is an integer of at least 2.

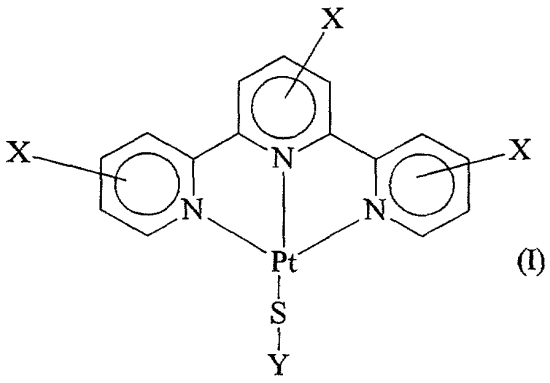
7. A compound as claimed in any one of claims 1 to 5 which is

2-hydroxyethanethiolate-(2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanethiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanthiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),
2-hydroxyethanthiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
2-aminoethanethiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-2-thiolate-(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II),

pyridine-4-thiolate-(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II),
pyridine-4-thiolate-(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-chloro-2,2':6',2"-terpyridine)platinum (II),
pyrimidine-2-thiolate-(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II),
imidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-butyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-hexyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-n-octyloxy-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-bromophenyl-2,2':6',2"-terpyridine)platinum (II)],
imidazole-2-thiolate-bis[(4'-p-tolyl-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)],
benzimidazole-2-thiolate-bis[(4'-ethoxy-2,2':6',2"-terpyridine)platinum (II)],
N,S-bis[(2,2':6',2"-terpyridine)platinum(II)] thioacetimine,
N,S-bis[(4'-chloro-2,2':6',2"-terpyridine)platinum (II)] thioacetimine,
diethylphosphorothioato (4'-chloro-2,2':6',2"-terpyridine)platinum(II),
succinylthiolatoplatinum (II) 2,2':6',2"-terpyridine, or
1-thio-β-D-glucose(2,2':6',2"-terpyridine)platinum (II).

8. Use of a compound as defined in any one of the preceding claims in the manufacture of a medicament for use as an anti-protozoal, anti-rheumatoid arthritic or anti-tumour agent.

9. A compound which is a complex of formula (I)



(I)

wherein

each X, which may be the same or different, is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, aralkyl, alkaryl, acyl, halogen, haloalkyl, haloaryl, hydroxyalkyl, hydroxyaryl, aminoalkyl, aminoaryl, primary, secondary or tertiary amine, hydrazine, alkylhydrazine, alkoxyl, aralkoxyl, nitrile, ester, amide, nitro, azide or aziridino, or is a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species, or a covalently linked moiety which provides recognition for a target receptor; and

Y is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aralkyl, heterocyclyl, an inorganic oxyacid or inorganic oxyacid derivative, or a covalently linked chain which is joined to at least one other complex of formula (I) so as to form a dimeric or oligomeric species; or

a pharmaceutically acceptable salt thereof, with the proviso that the complex of formula (I) is not 2-hydroxyethanethiolate(2,2':6',2"-terpyridine)platinum (II) or 2-aminoethanethiolate(2,2':6',2"-terpyridine)platinum (II).

10. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 7 or 9 in association with a pharmaceutically acceptable carrier or excipient.

Rev. 3-21-01

Effective March 1998

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

( ) Original ( ) Supplemental ( ) Substitute (X) PCT ( ) DESIGN

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: PLATINUM (II) COMPOUNDS

of which is described and claimed in:
( ) the attached specification, or
( ) the specification in application Serial No. _____, filed August 24, 2001, and with amendments through _____, or
(X) the specification in International Application No. PCT/GB00/00686, filed February 25, 2000, and as amended on _____(if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Great Britain	9904523.9	February 26, 1999	Yes

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys and agents named herein to accept and follow instructions from J.A. Kemp & Co. as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

ATTACHMENT A

Direct Correspondence to Customer No:	Direct Telephone Calls to:
000513 PATENT TRADEMARK OFFICE	WENDEROTH, LIND & PONACK, L L P 2033 "K" Street, N W , Suite 800 Washington, D.C 20006-1021 Phone (202) 721-8200 Fax (202) 721-8250

Full Name of First Inventor	FAMILY NAME LOWE	FIRST GIVEN NAME Gordon	SECOND GIVEN NAME	
Residence & Citizenship	CITY Oxford	STATE OR COUNTRY Great Britain	COUNTRY OF CITIZENSHIP Great Britain	
Post Office Address	ADDRESS c/o University of Oxford, Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, GREAT BRITAIN	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Second Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Third Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Fourth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Fifth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

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Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1st Inventor _____ Date _____
Gordon LOWE

2nd Inventor _____ Date _____

3rd Inventor _____ Date _____

4th Inventor _____ Date _____

5th Inventor _____ Date _____

6th Inventor _____ Date _____

The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date August 24, 2001

Applicant Reference Number N.75979B Atty Docket No. 2001-1187A

Title of Invention PLATINUM (II) COMPOUNDS

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

( ) Original ( ) Supplemental ( ) Substitute (X) PCT ( ) DESIGN

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: PLATINUM (II) COMPOUNDS

of which is described and claimed in:
( ) the attached specification, or
( ) the specification in application Serial No. _____, filed August 24, 2001, and with amendments through _____, or
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I hereby authorize the U.S. attorneys and agents named herein to accept and follow instructions from J.A. Kemp & Co. as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

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Full Name of Fifth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP
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Full Name of Sixth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
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1st Inventor ______________________ Date 09-11-01
Gordon LOWE

2nd Inventor ______________________ Date __________

3rd Inventor ______________________ Date __________

4th Inventor ______________________ Date __________

5th Inventor ______________________ Date __________

6th Inventor ______________________ Date __________

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Applicant Reference Number N.75979B Atty Docket No. 2001-1187A

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